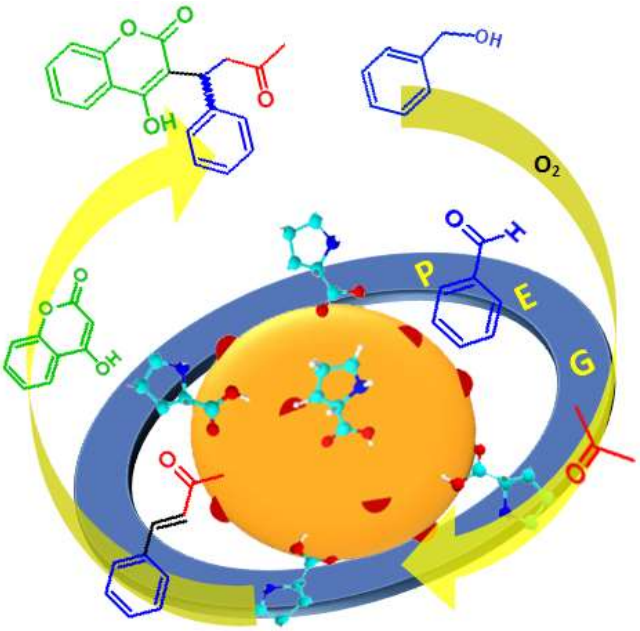
Chapter 3

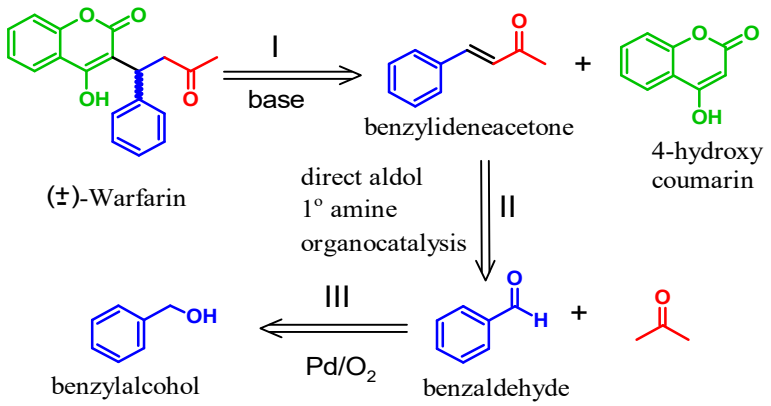
Fe_3O_4@L-proline/Pd Nanocomposite for One Pot Tandem Catalytic Synthesis of (±) - Warfarin from Benzyl Alcohol: Synergistic Action of Organocatalyst and Transition Metal Catalyst



Published in: ***Catalysis Science & Technology***, 2019,**9**, 6517-6531

3.1 Introduction

Warfarin (Coumadin® or Marevan®) is an anticoagulant drug most commonly prescribed by physicians for the prevention of thrombosis and embolism. It functions by inhibiting the vitamin-K mediated biosynthetic pathway leading to the formation of blood-clotting proteins. Most commonly, it is synthesized by Michael addition of 4-hydroxycoumarin to benzylideneacetone in presence of a base. Various organocatalyst having primary amines, amino acid functionalities and natural cinchona derived chiral amines and diamines are reported to favor the asymmetric synthesis of one of the enantiomers.[1 -4] The S-enantiomer is shown to be 2-5 times more active than the R enantiomer. Moreover, it has a different metabolic pathway in the human and also has lesser half-life than the R enantiomer (21-40 h for S and 37-89 h for R-warfarin).[5 -7] However, in general, it is prescribed in the racemate form [1, 5] and its dosage is adjusted on 'individual basis' considering the patient's disease history. Herein, we have attempted to synthesize (±)-warfarin from scratch in a one pot synthesis by a 3-way catalysis! that is by (1) oxidizing benzyl alcohol to aldehyde level, then (ii) condensing the latter with acetone directly in an aldol fashion leading to benzylideneacetone (iii) it is then condensed with 4-hydroxycoumarin resulting into the target racemic product (Scheme 1), by developing catalytic nanocomposite. Properly designed nanocomposite material can do its function effectively and efficiently.



Scheme 1: Planning for one pot synthesis of (±)-warfarin from benzyl alcohol through 3-way catalysis by using single nanocomposite catalyst having multiple components (I, II and III).

Controlled oxidation of benzyl alcohol to benzaldehyde level is very well reported in literature.[8,9] Many oxidizing agents are explored for the purpose. For example, stoichiometric

quantity of Cr (VI) (John's reagent, Collins reagent, PCC, PDC etc.), Mn (VII) (aqueous, acidic or basic solution of $KMnO_4$), Os (VIII) (OsO_4), Ru (VI, VIII) (RuO_4) metal based reagents are all used for the purpose.[10] Attempts have also been made to use H_2O_2 or O_2 as oxidant for neat, clean and atom efficient oxidation process.[11 -15] These oxidants work in presence of early transition metals with d^0 configuration like Mo (VI), W (VI), Ti (V) or Pd (II) complexes. However, these methods involve chlorinated solvents and generate metallic salts as solid waste that are toxic and pollute the environment. Oxidation methods mediated by TEMPO (2, 2, 6, 6-tetramethylpiperidine-1-yloxyl) and related stable nitroxide radicals (Anelli oxidation) [16] have also been developed. However, these methods contain bleach (NaOCl) and HOCl which are generated in situ that harm the environment.[17] Hence, the development of the neat, clean and atom efficient oxidation processes are the need of the day.[18, 19] From the mechanistic points of view, above oxidizing agents donate 'O' atom, an intrinsic part of their molecular structure, to the substrate and oxidize it. However, the same function can be carried out by using pure O_2, air or peroxides (H_2O_2 will be the best) as an oxidant for 'green' oxidation processes. But, the molecular oxygen in a ground state (triplet state) is 'inactive' and needs to be activated to act as an oxidizing agent.[20] This requires early transition metals with d^0 configuration (as mentioned above) and their complexes with sterically hindered ligands like PPh_3 mediated catalysis. For example, R. A. Sheldon group developed a water soluble Pd(II) bathophenanthrolin complex for selective aerobic oxidation of wide range of alcohols to aldehyde, ketones and carboxylic acids in a biphasic water-alcohol system. The use of water as a solvent and air as the oxidant made the process economical and environment friendly.[15] However, as the catalyst is water soluble, there is a chance of loss of precious Pd metal during catalyst recovery. A number of efforts have been made on Au-based materials for alcohol oxidation. For example, T. Saleh group developed a series of NCs made of Pd and Au NPs supported on carbon (Au-Pd/C), prepared by impregnation and solvent immobilization techniques. These catalytic NCs were evaluated for solvent-less oxidation of benzyl alcohol to benzaldehyde in liquid phase by using 35% H_2O_2 as an oxidizing agent. They were able to achieve 88% selectivity for the target oxidation in presence of Au-Pd/C NCs prepared by impregnation method. Enache et al. developed Au@Pd core-shell supported on TiO_2 matrix for oxidation of 1° alcohol to aldehyde with O_2 as oxidant at 373 K. They obtained very high TOF (270,000 per h) from the process.[21] However, it is too costly and commercially unviable. It is established that recovery of Pd becomes efficient when it is

anchored/doped/supported on a solid matrix which is magnetic or superparamagnetic in nature. Zamini et al reported a Pd/Fe_3O_4/amino acid nanocomposite. They obtained more than 99% selectivity for benzyl alcohol to benzaldehyde in solvent free conditions.[22] Wang et al prepared Pd supported on Al_2O_3 and TiO_2 by wet impregnation method and used it as a catalyst for solvent-free selective oxidation of benzyl alcohol by molecular oxygen. The developed catalyst showed high activity and selectivity for benzaldehyde on pretreatment like calcination.[23]

Drawing inspiration from these works and considering the need for the recovery of the precious metal catalyst without any loss, it was planned to load the metallic Pd on the surface of magnetic Fe_3O_4 nanoparticles (NPs) in present study.

Generally, aldol condensation requires base (dil. NaOH) catalyst and activation of substrates to react in a desired way to form C-C bond.[24, 25] It takes place in two steps namely aldolization and dehydration. Practically, with a stronger base, high temperature and longer reaction time, the aldol product can get dehydrated to form α, β – unsaturated carbonyl compound. The development of direct catalytic asymmetric aldol reaction (limited to first step) under mild conditions in presence of L-proline like amino acids as organocatalyst,[26] aldolase enzyme [27] or catalytic antibodies [28] in a 'green solvent' like water is a subject of research and reported very well in the literature. For the present, required strategy for one pot synthesis of warfarin, aqueous solution of base cannot be used due to its chance of attacking the Fe_3O_4 base matrix. List, Learner and Barbas for first time reported enamine based organocatalyst for asymmetric aldol reaction.[29] Encouraged by this, a strategy was devised such that L-proline can be loaded on to the surface of Fe_3O_4 either by using carboxylic acid group as 'handle' or by H-bonding with surface oxygen atom leaving the secondary imine group, the catalytic site, free. The loading of L-proline on to the Fe_3O_4 surface would serve two purposes (i) it would provide a catalytic site for aldol reaction which can be further proceeded to α, β – unsaturated ketone by adjusting the time and temperature of the reaction (ii) it can also serve as a base required in catalytic amount for final condensation with coumarin in step III.

It can be concluded from the above discussion that for the development of a green one pot tandem catalytic process for the production of (±) – warfarin from benzyl alcohol, the following parameters should be taken care of: (i) sufficient Pd sites should be available on the surface of magnetic matrix (ii) there are chances of formation of by-products like carboxylic acid, esters, or ethers in the first step, dibenzylideneacetone (dimer) in the second step and

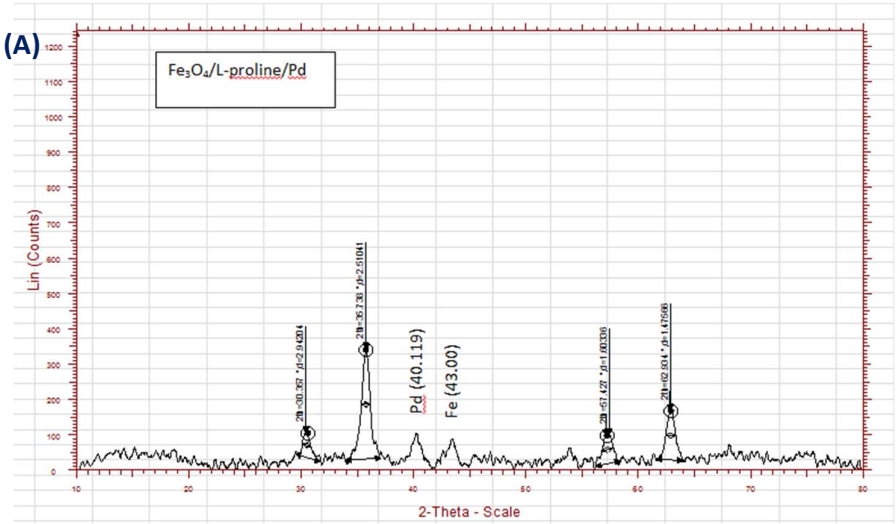
other condensation products in the third step, which should not interfere during the reaction or in the preceding steps (iii) there should be an immediate desorption of products from the surface and should not block the catalytic sites (iv) the product of the first step should easily be available as a reactant for the second step and so on for the continuation of the tandem process (v) the selection of the solvent system for this tandem process is crucial and it should be compatible with all the reaction components, should be green in nature as well as recyclable (vi) corrosion of the matrix and the leaching of the catalytic components should be monitored throughout the process. All these aspects can be set by process optimization. Overall, economic and ecological aspects should be considered for the development of the one pot multi-stage organic transformations on industrial scale.

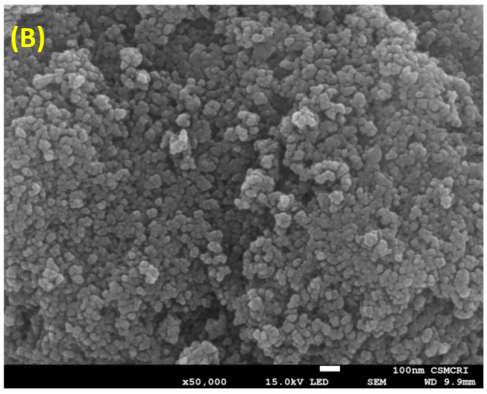
The purpose of this work is to develop a tandem one pot catalytic process involving a cascade of chemical reactions carried out by using 'green solvents and reagents' leading to racemic warfarin. For this, we have developed Fe_3O_4@L-proline/Pd nanocomposite (NCs) and used it as single catalyst for the proposed tandem process beginning from benzyl alcohol. The process parameters like temperature, reaction time, solvent and the stoichiometry of the reagents required at each stage are optimized considering the environmental aspects.

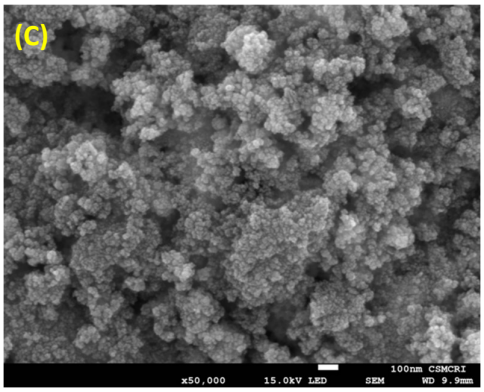
3.2 Results and Discussion

The synthesized L-proline capped Fe_3O_4 NPs were characterized by XRD to confirm phase, purity, particle size and crystallinity of the material (Fig. 1A). The XRD pattern manifests predominant diffraction peaks at 2θ values 30.39, 35.67, 43.36, 53.50, 57.26 and 62.92 corresponding to the (200), (311), (400), (422), (511) and (440) planes respectively (JCPDS 82-1533) confirming magnetite phase of Fe_3O_4. Magnetite phase is known for its inverted spinel structure having face centered cubic (FCC) arrangement and Fe cations occupying the interstitial Td and/or Oh sites. The particle size was calculated from Debye-Schirrer formula ($L=0.9\lambda/\beta\cos\theta$) [30] and the FWHM (Full Width at Half Maximum) value of major peak for (311) planes, in the range of 10 nm. On introduction of Pd in Fe_3O_4@L-proline NPs, new peaks at 2θ values 40.12, 40.65 and 68.12° emerged corresponding to (111), (200) and (220) planes of Pd, respectively (JCPDS 46-1043). The major peak at 40.12° due to (111) planes has high intensity while the other two peaks merge into the background noise due to very less amount of Pd in the host matrix. This confirms Pd metal in zero oxidation state (also, due to hydrazine-a

reducing agent-used to load Pd on the host matrix). The emergence of new peaks in the XRD pattern on loading Pd indicates the presence of Pd as a separate phase in the form of small islands on the host surface which can act as catalytic sites for organic transformations. Further, the size and shape of pristine Fe_3O_4, Fe_3O_4@L-proline NPs and Fe_3O_4@L-proline/Pd NCs were studied by TEM analysis (Fig. 1D and 1E). The TEM images show spherical particles and most of the particles are present in the size range of 100 – 150 nm. The spots having equal intensity in Selected Area Electron Diffraction (SAED) indicate the highly crystalline nature of the material. The lattice fringes of exposed (311) planes of Fe_3O_4@L-proline, revealed 10 nm distances among the planes which were almost maintained on Pd loading. From the TEM images and SAED patterns it can be concluded that L-proline organic layer and Pd loading did not alter the lattice parameters of the host Fe_3O_4 retaining the crystallinity of the material which is necessary for the catalytic activity and recycling ability due to magnetic nature of the material.







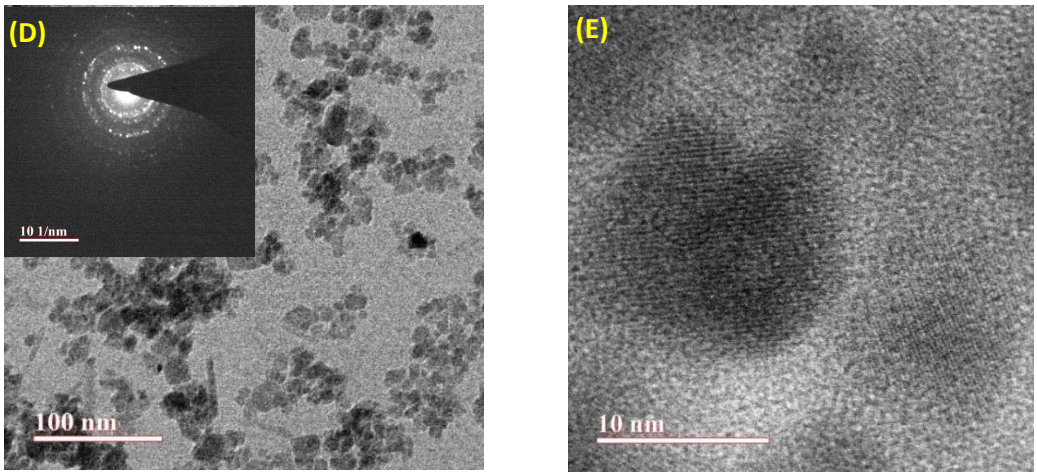


Fig. 1. (A) XRD pattern (B) and (C) SEM image (D) TEM image. Inset image shows SAED pattern and (E) lattice fringes of as-synthesized Fe_3O_4@L-proline/Pd NCs.

FTIR spectroscopy is one the best tools to study the interaction of ligand molecules with the host surface atoms. [31-33]

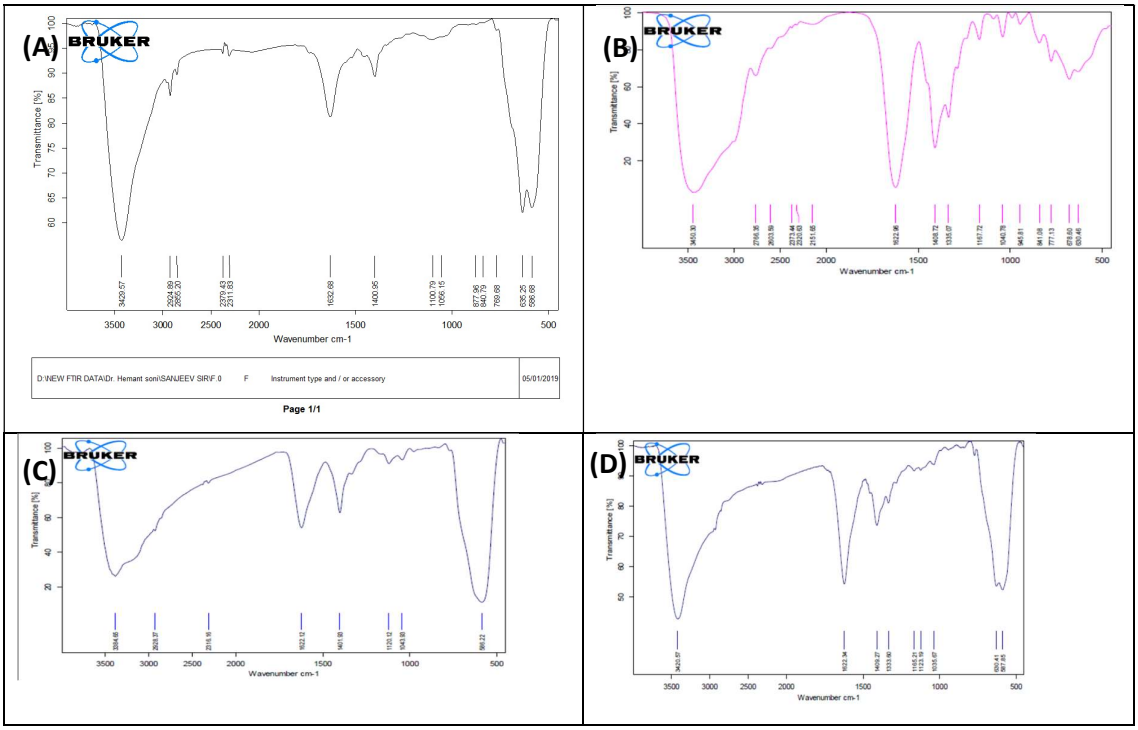


Fig. 2. FTIR spectra of (A) blank Fe_3O_4 (B) L-proline (C) Fe_3O_4@L-porline and (D) Fe_3O_4-L-porline/Pd.

Fig. 2B shows the FTIR spectrum of L-proline. The vibration at 1622 and 1428 cm^{-1}correspond to ν_{as} and ν_s carboxylate stretching respectively, while the hump at 1335 cm^{-1} to –OH bending in carboxylic acid when it is in free form. When L-proline interacts with Fe_3O_4, (Fig. 2C and 2D) this hump disappears keeping other carboxylate stretching vibrations maintained intact suggesting that L-proline molecules orient on the surface of Fe_3O_4 by H-bonding with surface oxygen atoms (Fig. 3). The vibration at 636 cm^{-1} is due to Fe-O stretching. There is no subtle change in FTIR spectra when Pd is loaded on Fe_3O_4@L-proline.

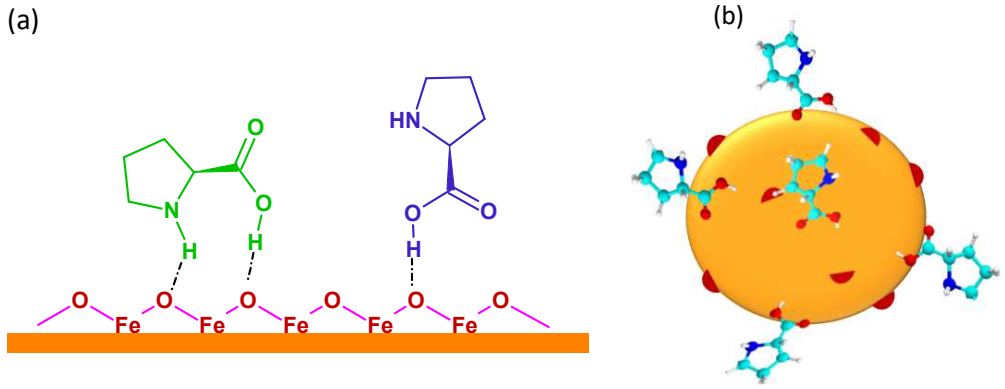
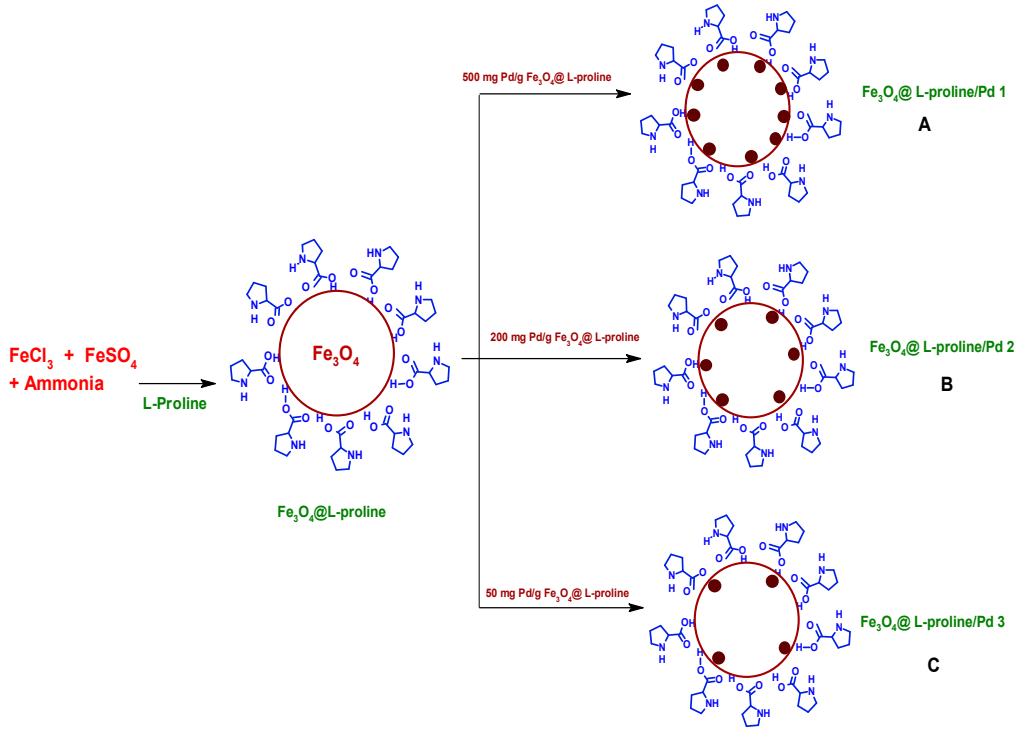
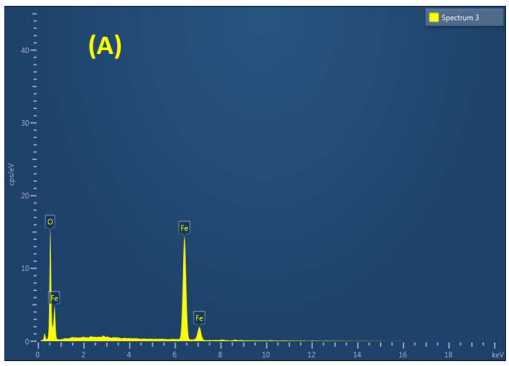


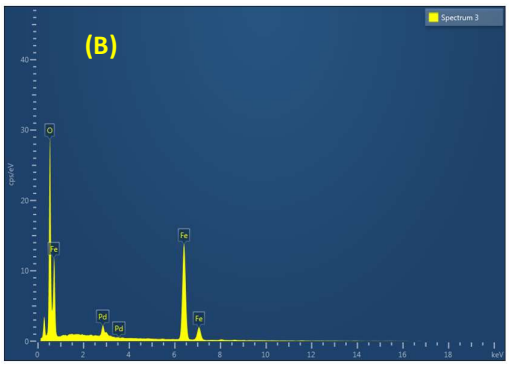
Fig. 3. Interaction of L-proline molecules with Fe_3O_4 NPs surface (a) through H-bonding, revealed from FTIR spectroscopy and (b) cartoon showing overall molecular frame-work of the multicomponent catalyst deduced from FTIR spectroscopy and XRD analysis. Small dark-brown semi-spheres show Pd islands on the surface of host Fe_3O_4 NPs

As discussed earlier, 3-way catalysis is required for the one pot synthesis of (±)-warfarin from benzyl alcohol. The benzylideneacetone formed by α-alkylation of ketone with 1° alcohol in two steps can be directly condensed with 4-hydroxycoumarin under mild basic condition in a single pot. For the purpose, the amount of L-proline and Pd loaded on to the surface of host Fe_3O_4 must be optimized. Stoichiometric amount of L-proline was used as capping agent during the synthesis of Fe_3O_4 NPs. Hence, the amount of Pd loaded on the surface of Fe_3O_4@L-proline was varied. Accordingly, three sets of Fe_3O_4@L-proline/Pd NPs were prepared (Scheme 2) and used for optimization of alcohol/ketone condensation reaction leading to benzylideneacetone in one pot. The amount of Pd loaded was also determined from elemental EDAX analysis (Fig. 4).



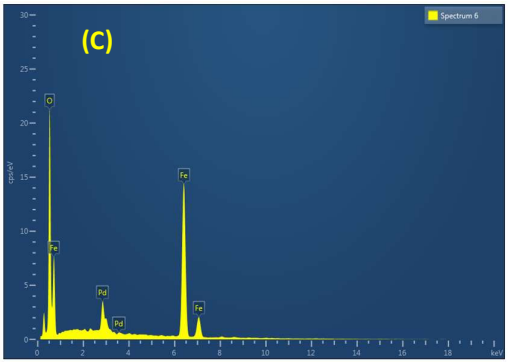
Scheme 2: Stoichiometric distribution of Pd metal on surface of L-proline capped Fe_3O_4 NPs.

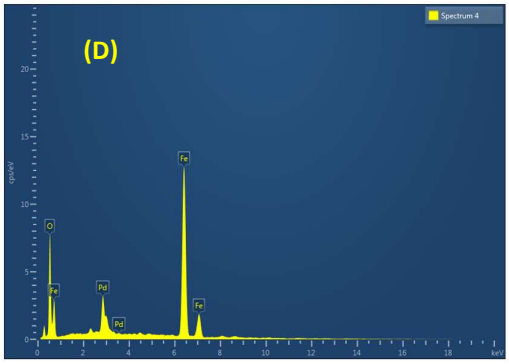




Element	Line Type	Wt%	Atomic %
O	K series	26.31	55.49
Fe	K series	73.69	44.51
Total:		100	100

Elemen	Line Type	Wt%	Atomic %
O	K series	40.47	71.1
Fe	K series	55.11	27.74
Pd	L series	4.41	1.17
Total:		100	100





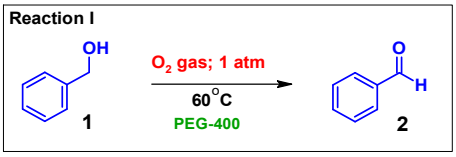
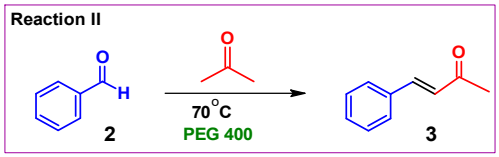
Element	Line Type	Wt%	Atomic %
O	K series	34.83	66.4
Fe	K series	57.49	31.4
Pd	L series	7.68	2.2
Total:		100	100

Element	Line Type	Wt%	Atomic %
O	K series	20.44	48.84
Fe	K series	69.45	47.53
Pd	L series	10.11	3.63
Total:		100	100

Fig. 4. EDAX elemental analysis of as-synthesized (A) Fe_3O_4@ L-proline (B) Fe_3O_4@ L-proline/Pd 3 (C) Fe_3O_4@ L-proline/Pd 2 (D) Fe_3O_4@ L-proline/Pd 1 NPs.

It can be observed from Table 1 that Fe_3O_4@L-proline/Pd1 having maximum amount of Pd loaded (A, 500 mg/g NPs) can convert **1** to **2** in 32 h in presence of O_2 gas at 1 atm and 60 ^{o}C in PEG-400 medium, but it failed to transform **2** into **3** in a separate reaction. This may be due to the blocking of the catalytic imine site of L-proline with excess Pd. When Fe_3O_4@L-proline/Pd3 NPs having very less amount of Pd loaded (C, 50 mg/g NPs) was used as catalyst, the first conversion **1** to **2** could not take place in measurable amount while it could convert **2** to **3** within 20 h when the reaction was carried out separately. Optimum performance could be achieved in presence of Fe_3O_4@L-proline/Pd2 (B, 200 mg Pd/g NPs); it was able to transform **1** to **2** in 60 h and **2** to **3** in 24 h in separate reactions. Hence, Fe_3O_4@L-proline/Pd2 was selected to proceed further.

Table 1. Reactions optimization in presence of as-synthesized catalytic nanocomposite having different amount of Pd loading.[a]

Catalyst System	Amount[b] of Pd mg/g NCs	Reaction I 	Reaction II 
A	500	Reaction completed in 32 h.	No reaction
B	200	Reaction completed in 60 h.	Reaction completed in 24 h.[c]
C	50	No reaction	Reaction completed in 20 h.

[a] Aerial oxygen is not sufficient to complete the reaction.

[b] Theoretical amount. Actual amount varies in same proportion as determined from EDX elemental analysis (Fig 4).

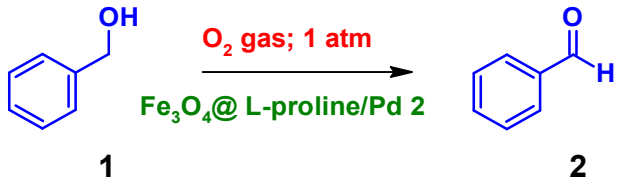
[c] ±0.5 h. The progress of reaction was monitored on TLC plate after every half an hour and the reactions were carried out in triplicate.

3.2.1 Screening of solvent. Both the processes namely, oxidation of benzyl alcohol to benzaldehyde (**1** to **2,** Reaction-I) and condensation of benzaldehyde with acetone to benzylideneacetone (**2** to **3,** Reaction-II) were carried out separately in presence of as-synthesized NCs as catalyst for solvent screening to achieve optimum conversion by considering the 'green aspects'. The best choice for the purpose is to carry out the transformations in water as a medium. It can be observed from Table 2 that Reaction-I was successfully carried out in water, about 70% yield of **2** was achieved in 96 h at RT; however, no reaction took place for Reaction-II in water at RT up to 70 °C. Similar results were obtained when both the reactions were carried in toluene as a solvent. Also, both the reactions were unable to proceed separately at RT in ethanol as reaction medium. We had also carried out the reactions in PBS buffer at neutral pH 7.4. Interestingly, 76% conversion was achieved at RT within 60 h for Reaction-I, however, it was unable to support Reaction-II separately although continued till 2 days. On literature survey, we found that PEG-400 is a low cost, non-toxic and eco-friendly liquid polymer and in addition, it can be recovered by extraction with a suitable solvent or by direct distillation of water or solvent. [34, 35] It can act as recyclable

reaction medium for Baylis-Hillman reaction,[36] Heck reaction[37] and asymmetric dehydroxylation.[38] It also supports aldol condensation reaction by acting as catalyst with anhydrous K_2CO_3.[39] S. Chandrasekhar et al reported L-proline catalyzed asymmetric aldol reaction in PEG-400 as a recyclable medium.[40] They were able to recycle this solvent 10 times without losing the activity of the L-proline catalyst. In the present case, when PEG-400 was used as a solvent for Reaction-I, it was unable to support the oxidation of **1** to **2** at RT though the reaction was continued for 4 days; however, it could complete the reaction at 60 ^{o}C to almost 90% conversion within 3 days (Table 2). Similar results were observed for Reaction-II for aldol condensation of **2** to **3** with acetone (Table 3). PEG-400 was not able to sustain this reaction at RT up to 40 ^{o}C when the reaction was continued for 2 days, but could drive the reaction to 53% yield at 70 ^{o}C within 24 h (Table 3). Hence, it is established that PEG-400 is suitable as solvent for one pot α-alkylation of acetone with benzyl alcohol. It can be assumed that the Reaction-II may proceed via β-hydroxyketone, but it directly condensed into **3** due to dehydration at high temperature.

Table 2. Optimization of solvent system and temperature for Reaction-I in presence of as-synthesized Fe_3O_4@L-proline/Pd 2 NCs.

Reaction I

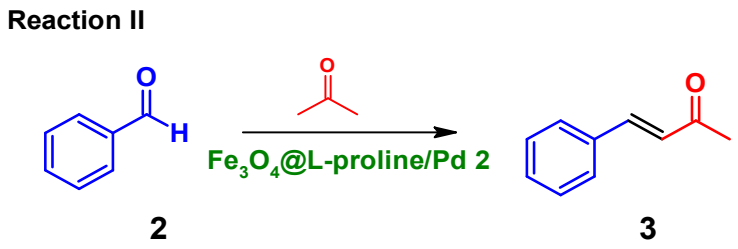


Solvent	Time[c], h	Temperature, °C	yield[a,b], %
Toluene	48	70	56
Ethanol	48	RT	Trace
PBS buffer 7.4 pH	60	RT	76
Water	96	RT	70
PEG-400	96	RT	Trace
PEG-400	60	60	94

[a] Isolated yields after column chromatography. The reactions were carried out in triplicate. [b] Benzyl alcohol (1.0 mmol), solvent (5 mL) and catalyst (100 mg) were stirred at above mentioned temperature under 1 atmospheric pressure of dioxygen in a sealed tube, till the disappearance of starting material (from TLC plate). The product was extracted in diethyl ether (10mLx 3), concentrated and purified by column chromatography eluting with cyclohexane/ethylacetate.

[c] ±0.5 h. The progress of reaction was monitored on TLC plate after every half an hour.

Table 3. Optimization of solvent system and temperature for Reaction-II in presence of as-synthesized Fe_3O_4@L-proline/Pd 2 NCs.



Solvent	Time, h	Temperature, °C	yield[a,b], %
Toluene	24	70	No reaction
Ethanol	24	RT	No reaction
PBS buffer 7.4 pH	24	RT	No reaction
PBS buffer 7.4 pH + DMSO	24	RT	No reaction
Water	24	RT	No reaction
Water	24	39	16
PEG 400	24	40	Trace
PEG 400	24	70	53

[a] Isolated yields after column chromatography. The reaction was carried out in triplicate for 24h.

[b] Benzaldehyde (1.0mmol), acetone (5 mL), and catalyst (100 mg) in 5 mL of above solvent were stirred at ambient temperature in a sealed tube till disappearance of the starting material (from TLC plate). The product was extracted in diethyl ether (10mLx 3), concentrated and purified by column chromatography eluting with cyclohexane /ethyl acetate.

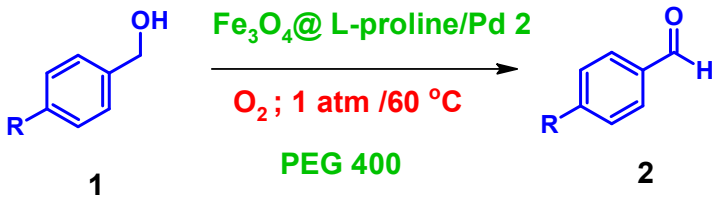
3.2.2 Screening of substrate. Different derivatives of benzyl alcohol were evaluated for both Reactions-I and II separately to understand the electronic effect of substituent group on the reaction (Table 4 and 5). p-Nitro benzyl alcohol could not undergo oxidation under optimized

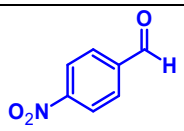
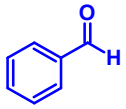
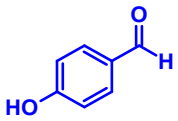
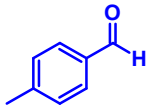
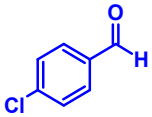
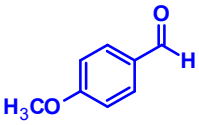
reaction parameters (O_2, 1 atm/ 60 ^oC, PEG-400) and resulted in poor yield (15%) within 3 days while, 53% yield was obtained for Reaction II under optimized parameters (acetone, 70 ^oC, PEG-400) within 2days. When electron releasing –OH group was attached to benzyl alcohol, Reaction I was completed within 60 h with almost 90 % yield. However, it was unable to carry out aldol condensation even though the reaction was continued for 2 days. It is interesting to note that p-OCH_3, p-CH_3 and p-Cl attached to benzyl alcohol can undergo both the reactions (separately) with substantial per cent yields (entry 4, 5 and 6, Table 4 and 5) in 60 and 48 h for reaction I and II, respectively. Unsubstituted benzyl alcohol undergoes oxidation with highest (94%) yield in 60 h while, its corresponding aldehyde can condense with acetone at 70 ^oC in PEG-400 medium to form **3** within 48 h and 53% conversion in a separate reaction (Table 4, 5 entry 2).

From the above observations, benzyl alcohol was selected to begin with, to carry out both Reaction-I and II in a single pot in presence of Fe_3O_4@L-proline/Pd2 NCs as catalyst and PEG-400 as solvent. It can be seen from Table 6 that benzyl alcohol yields corresponding benzylideneacetone at the end of 5th day with 47% yield while, p-CH_3, p-Cl and p-OCH_3 derivatives of **1** yield 52, 52 and 58% overall conversion to **3** at the end of the 5th day in one pot.

In next set of experiments, the above two steps were extended to the third sequential reaction, that is the Michael addition of 4-hydroxycoumarin (**4)** to **3**. The pot reaction was extended for further 12 h at 100° C maintaining the other pot conditions same (Scheme 3). At the end of 6th day (overall 132 h), (±) – warfarin could be separated by fractional crystallization from the reaction mass with 35% yield. The peculiarity of this one pot one catalyst process is that the solvent PEG-400 can be recycled (3 times in this study) to carry out fresh pot reaction without the loss of catalytic activity.

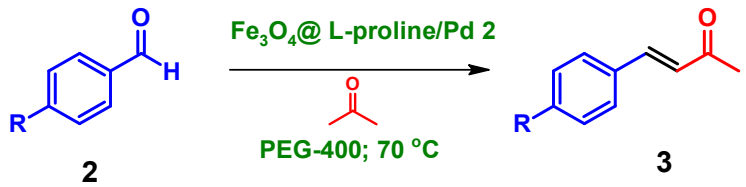
Table 4. Oxidation of benzyl alcohol and it derivatives to corresponding aldehyde (Reaction-I) under optimized reaction parameters in presence of Fe_3O_4@L-proline/Pd 2 NCs.

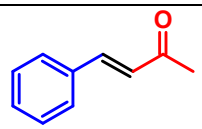
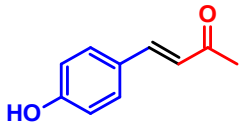
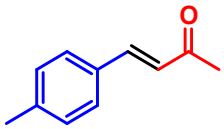
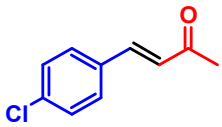
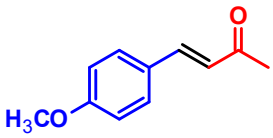
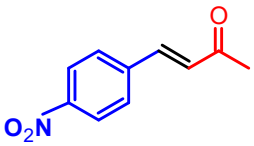


-R	Time(h)	Product	Yield[a] (%)
$-NO_2$	60		15
-H	60		94
-OH	60		90
$-CH_3$	60		92
-Cl	60		80
$-OCH_3$	60		78

[a] Isolated yields after column chromatography.

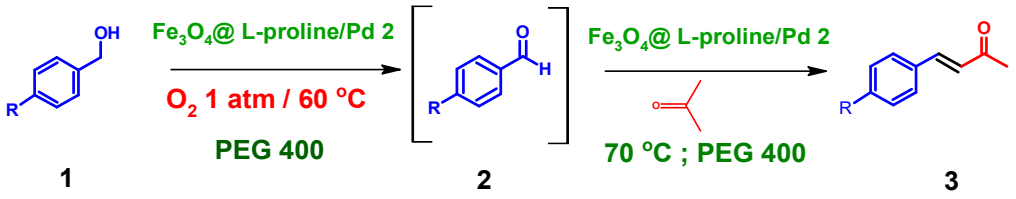
Table 5. Aldol condensation of benzaldehyde and its derivatives to corresponding benzylideneacetone (Reaction-II) under optimized reaction parameters in presence of Fe_3O_4@L-proline/Pd 2 NCs.

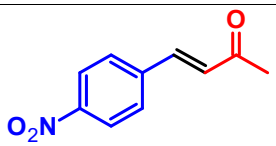
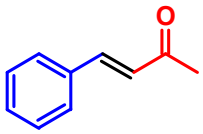
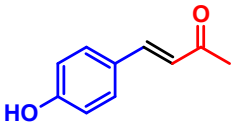
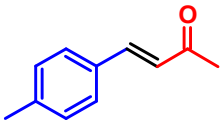
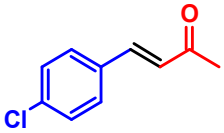
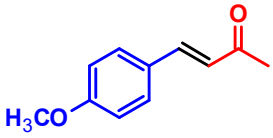


-R	Time, h	Product	Yield[a], %
-H	24		53
-OH	24		No reaction
-CH_3	24		58
-Cl	24		68
-OCH_3	24		65
-NO_2	24		No desired product

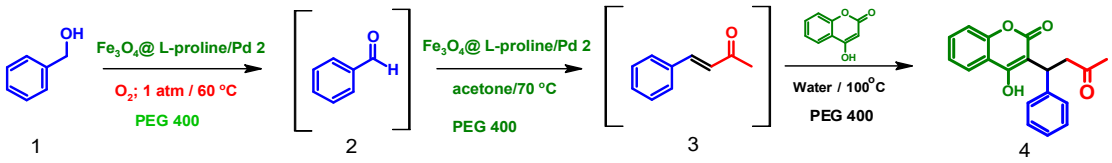
[a] Isolated yields after column chromatography.

Table 6. One pot conversion of benzyl alcohol and its derivatives to benzylideneacetone in presence of Fe_3O_4@L-proline/Pd 2 NCs under optimized reaction parameters.



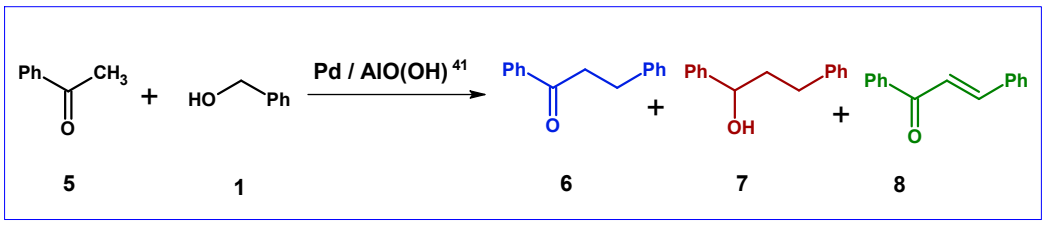
-R	Time, h	Product	Yield[a], %
$-NO_2$	60 + 24		No product
-H	60 + 24		47
-OH	60 + 24		No product
$-CH_3$	60 + 24		52
-Cl	60 + 24		52
$-OCH_3$	60 + 24		58

[a] Isolated yields after column chromatography.



Scheme 3. Synthesis of (±)-warfarin through 3-way catalysis in presence of Fe_3O_4@L-proline/Pd 2.

3.2.3 Discussion. Park et al.[41] reported palladium (0.2mol%) nanoparticles entrapped in aluminium hydroxide, Pd/AlO(OH). This catalyst shows activity for alkene hydrogenation and aerobic alcohol oxidation. It produced 1,3-diphenylpropan-1-one (**6**) in 97% yield in α-alkylation of acetophenone **5** with 1.2 equiv. of **1** in presence of a base like K_3PO_4 (3 equiv.) for 8 h at 80° C under Argon (Scheme 4). It produced chalcone **8** with a yield of 95% in 20 h when the reaction was carried out under 1 atm O_2 in a toluene medium. They compared the activity of the catalyst with different commercially available combinations like 5% Pd/C, 5% Pd/Al_2O_3, 5% $Pd/BaCO_3$, $[RuCl_2(PPh_3)_3]$, $[\{Ir(cod)Cl\}_2]$ etc. However, these catalysts favor **6** as the major product with very little formation of **7**. Product **8** was obtained in trace amounts or even none at all. On the contrary, the herein developed catalyst favors **8** as the major product due to step-wise reactions.



Scheme 4. Palladium-catalyzed coupling of acetophenone and benzyl alcohol in presence of Park's catalyst.[41]

Further, these catalytic processes require a base like K_3PO_4 (3 equiv.) or KOH (1 to 0.1 equiv.) for each cycle to reassume the reaction rate. Such strong bases may attack the host surface responsible for leaching of the precious metal catalyst. The Ru grafted hydrotalcite was reported to bring about α-alkylation of ketone to produce **6** without any requirement of a base. However, it demands very high temperature of 180° C.[42] Yanan et al have reported α-alkylation of acetone with **1** in presence of CrO_3 at 56° C in 10 h.[43] Apart from benzyl alcohol,

they selected p-OCH_3 and p-Cl derivatives as substrate and achieved high % yield of benzylideneacetone in agreement with our present results. They also obtained dibenzylideneacetone as by-product in various proportions. In this case, CrO_3 worked as oxidant as well as catalyst and got consumed at the end of the reaction. Hence, from the environmental point of view, this catalyst cannot be used on industrial scale. The importance of the presently developed catalyst is that it can do the 3-way catalysis leading to the (±)-warfarin in a single pot process in presence of all the products, by-products and intermediates generated during various reaction steps. The mechanism combining the transition metal catalysis and organocatalysis is shown in Fig. 5.

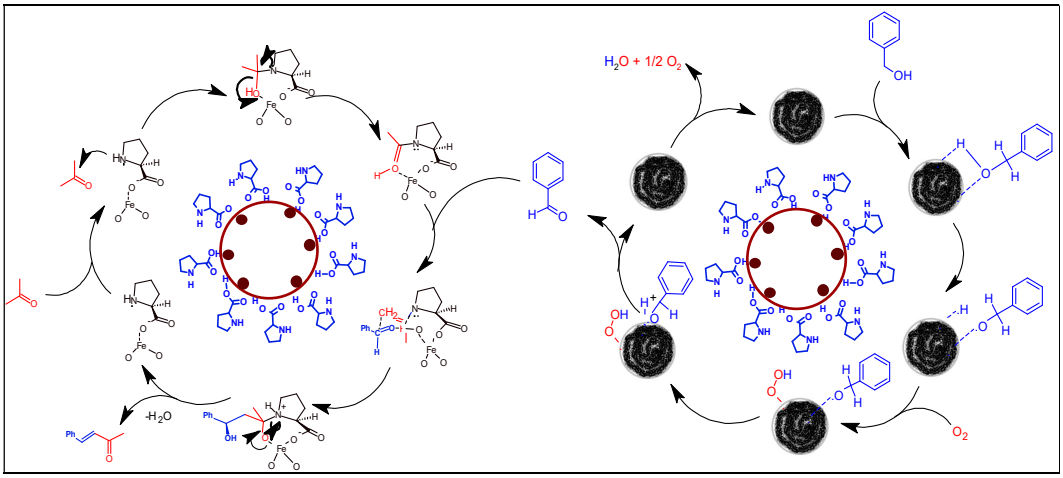


Fig. 5. The proposed mechanism for the conversion of (±) – warfarin starting from benzyl alcohol on the surface of multicomponent Fe_3O_4 NPs at various catalytic sites.

It is quite natural to think of chiral induction during step 3 of the tandem process due to the presence of L-proline on the surface as 2° amine organocatalyst to form enantiopure (R) or (S)-warfarin. Kristensen et al [44] had tested most common organocatalysts like MacMillion type imidazolidinone (**9**) and the Jørgensen/Hayashi diarylprolinols (**10,** Fig 6) for the synthesis of enantiopure warfarin. They achieved excellent per cent yield of racemic warfarin but poor conversion to a single specific stereoisomer even after 9 days. Jørgensen group [1] also carried out this reaction in presence of S-proline but they obtained only racemic warfarin as product. The possible reason, as explained by Kristensen, may be the long reaction time due to which the racemic pathway dominates over the asymmetric one.[44]

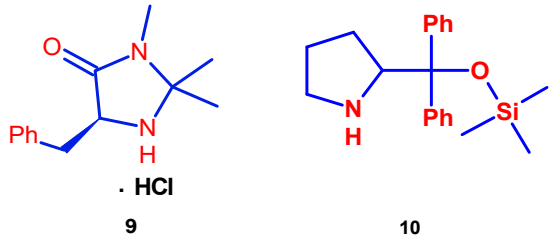


Fig. 6. Mac-Million type imidazolidinone (**9**) and Jørgensen/Hayashi diarylprolinols (**10**) organocatalysts.

To extend the application of the synthesized catalyst NCs and the developed one pot tandem reaction, we had carried out the reaction at pilot plant. The flow diagram of the unit processes used for the production of (±) – warfarin starting from 10 g of benzyl alcohol is shown in Fig. 7.

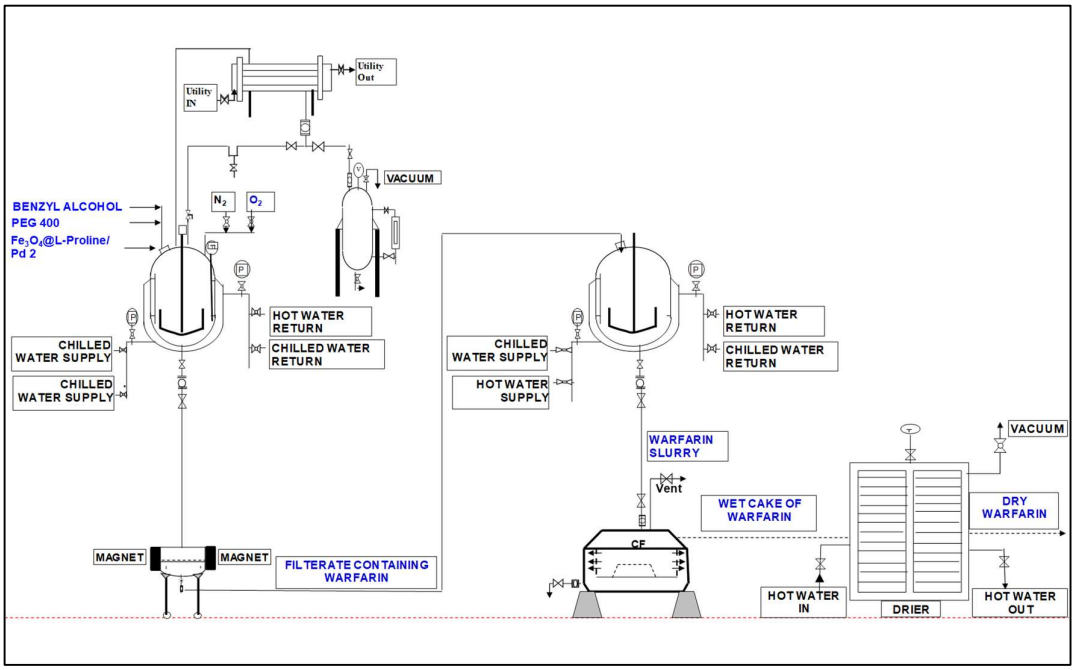


Fig. 7. Flow diagram for the pilot-scale production of (±) – warfarin from benzyl alcohol by developed tandem process in presence of Fe_3O_4@L-proline/Pd 2 NCs.

The procedure used for the production of target product in a tandem process at pilot plant is discussed in detail in the experimental section.

3.3 Experimental

All the chemicals were purchased from Aldrich Chemicals unless specified. $FeCl_3.6H_2O$ was purchased from Loba Chemie, India, $FeSO_4.4H_2O$was purchased from S. D. fine chemicals limited, India, Aqueous ammonia was purchased from S. R. Enterprise, India, L-Proline was purchased from TCI Chemicals and palladium acetate from Hindustan Platinum.

3.3.1 Synthesis of L-Proline coated magnetite nanoparticles (Fe_3O_4@L-proline NPs).

Amino acid coated magnetite nanoparticles were synthesized by the one pot synthesis method. In brief, 5.0 g of ferric chloride hexahydrate ($FeCl_3{\cdot}6H_2O$) and 2.4 g of ferrous sulphate tetrahydrate ($FeSO_4.4H_2O$) (molar ratio 1.75:1, respectively) were dissolved in 250 mL deionized water and the mixture was stirred vigorously under N_2 atmosphere at 70 ^oC. After 30 min, 5.3 g of L-proline was dissolved in 50 mL distilled water and rapidly added to the above mixture and the reaction was stirred for another 30 mins. Then 27 mL NH_4OH (25%) was rapidly added and stirring was continued for 1.5 h. The precipitates were separated magnetically, washed with distilled water three times, and dried in an oven at 100 °C overnight.

Dry weight of nanoparticles: 3.0 g

3.3.2 Synthesis of palladium loaded amino acid functionalized magnetite nanocomposite (Fe_3O_4@ L-proline/Pd NCs)

Palladium acetate (0.2 g) was dissolved in 200 mL of ethanol at room temperature. To this clear solution was added 1.0 g Fe_3O_4@L-proline NPs. This suspension was stirred vigorously and refluxed for 2 h. This dark suspension was cooled to room temperature and 2.5 mL, 80 % hydrazine hydrate ($NH_2NH_2{\cdot}H_2O$) was added. The reaction mass was further refluxed for 1.5 h. Prepared particles were separated magnetically, washed with ethanol three times followed by distilled water three times, and dried in an oven at 60°C overnight.

Dry weight of nanocomposite: 1.01g

3.3.3 Oxidation of benzyl alcohol (1) to benzaldehyde (2).

Benzyl alcohol (100 mg, 0.92mmol), PEG-400 (5.0 mL) and catalyst Fe_3O_4 @ L-proline/Pd NCs (100 mg) were stirred at pre-decided temperature under 1 atm dioxygen pressure in a sealed tube, till disappearance of the starting material (observed from TLC plate). The product was extracted in diethyl ether (10mLx 3), concentrated and purified by column chromatography, eluted with cyclohexane /ethyl acetate to yield a product as clear colourless liquid. (92 mg,

94%), mp 46-47 °C; ^{1}H NMR (300 MHz, $CDCl_3$-d1): δ (ppm). 7.48-7.53 (m, 2H), 7.58-7.64 (m, 1H), 7.85-7.88 (m, 2H) 10.00 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$-d1): δ (ppm). 128.39, 128.99, 129.70, 130.03, 134.45, 136.38, 192.38.

4-Chlorobenzaldehyde. Prepared as described for **2**. Starting from 4-chlorobenzylalcohol (100 mg, 0.70 mmol), after purification with silica gel column chromatography (cyclohexane/ethyl acetate) produced white solid (79 mg, 80%), mp 46-47° C; ^{1}H NMR (300 MHz, $CDCl_3$-d1): δ (ppm). 7.50-7.53 (m, 2H), 7.80-7.85 (m, 2H), 9.8 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$-d1) δ (ppm). 129.45 (2C), 130.90 (2C), 134.72, 140.92, 190.84.

p-Hydroxybenzaldehyde. Prepared as described for **2. S**tarting from 4-hydroxybenzylalcohol (100 mg, 0.80 mmol), after purification with silica gel column chromatography (cyclohexane/ethyl acetate) yielded light brown solid (88.5 mg, 90%), mp110-113°C. ^{1}H NMR (300 MHz, $CDCl_3$-d1): δ (ppm). 6.98-7.01 (m, 2H), 7.79-7.82 (m, 2H), 9.83 (s, 1H), 10.67 (brs, 1H). ^{13}C NMR (75 MHz, CDCl3-d1) δ (ppm) 116.66, 128.89, 132.54, 164.20, 191.31.

p-Methylbenzaldeyde. Prepared as described for **2**, starting from 4-methylbenzylalcohol (100 mg, 0.83 mmol) after purification with silica gel column chromatography (cyclohexane/ethyl acetate), Obtained as colourless liquid (90 mg, 92%); ^{1}H NMR (300 MHz, $CDCl_3$-d1) δ (ppm). 2.41 (s, 3H), 7.30 (d, 2H), 7.75 (d, 2H), 9.94 (s, 1H); ^{13}C NMR (75 MHz, CDCl3-d1) δ (ppm). 21.81, 129.08, 134.20, 145.51, 191.93.

p-Methoxybenzaldeyde. Prepared as described for **2**, starting from 4-methoxybenzyl alcohol (100 mg, 0.73 mmol), after purification with silica gel column chromatography (cyclohexane/ethyl acetate), obtained as colourless liquid (76 mg, 78%); ^{1}H NMR (300 MHz, $CDCl_3$-d1) δ (ppm). 3.82 (s, 3H), 6.94 (d, 2H), 7.76 (d, 2H), 9.82 (s, 1H); ^{13}C NMR (75 MHz, CDCl3-d1) δ (ppm). 55.58, 114.32, 129.94, 131.98, 164.62, 190.84.

p-Nitrobenzaldehyde. Prepared as described for **2**, starting from 4-nitrobenzyl alcohol(100 mg, 66 mmol), after purification with silica gel column chromatography (cyclohexane/ethyl acetate), obtained as yellow solid (15 mg, 15 %), mp102-104°C; ^{1}H NMR (300 MHz, $CDCl_3$-d1) δ (ppm). 8.10 (d, 2H), 8.41 (d, 2H), 10.18 (s, 1H); ^{13}C NMR (75 MHz, CDCl3-d1) δ (ppm). 124.32, 130.51, 140.06, 151.12, 190.37.

3.3.4 One pot synthesis of benzyl alcohol (1) to benzylideneacetone (3).

Benzyl alcohol (100 mg, 0.92 mmol) was added to PEG-400 (5 mL) and stirred for 10 min. Then, catalyst Fe_3O_4 @ L-Proline/Pd 2 NCs (100 mg) was added and stirred for 10 min. Further, this suspension was stirred for about 60 h at 60° C under 1 atmospheric pressure of dioxygen. After the disappearance of the starting material (confirmed from TLC plate), dioxygen flow was stopped and the reaction was flushed with N_2 gas. At this time, acetone (5 mL) was introduced and the reaction mixture was stirred for 5 min under inert atmosphere. The reaction vessel was sealed with a rubber septum and the mixture was stirred at 70° C for about 24 h. The product was extracted in diethyl ether (10mL x 3), concentrated and purified by column chromatography eluting with cyclohexane/ethyl acetate to give **3** as light-yellow low melting solid (64 mg, 47%). Rf 0.68 (1:3 Ethyl acetate/cyclohexane); ^{1}H NMR (300MHz, $CDCl_3$-d1) δ (ppm). 2.36(s, 3H), 6.70(d, 1H), 7.38(q, 3H), 7.49(s, 1H), 7.52(q, 2H). ^{13}C NMR (75 MHz, CDCl3-d1) δ (ppm). 27.49, 127.11, 128.28, 128.98, 130.55, 134.39, 143.51, 198.50.

4-methoxybenzelydeneacetone. Prepared as described for **3**; starting from 4-methoxybenzyl alcohol (100 mg, 0.73 mmol), after purification with silica-gel column chromatography (cyclohexane/ethyl acetate) obtained as white low melting solid (74 mg, 58%). Rf 0.65 (1:4 ethyl acetate/cyclohexane); ^{1}H NMR (300MHz, $CDCl_3$-d1) δ (ppm). 2.22(s, 3H), 3.70 (s, 3H), 6.47 (d, 1H), 6.78 (d, 2H), 7.34 (d, 1H), 7.36 (d, 2H); ^{13}C NMR (75MHz, CDCl3-d1) δ (ppm). 27.33, 55.32, 114.41, 124.93, 129.95, 143.22, 161.58, 198.29.

4-Chlorobenzyledeneacetone. Prepared as described for **3**; starting from 4-chlorobenzyl alcohol (100 mg, 0.70 mmol), after purification with silica gel column chromatography (cyclohexane/ethyl acetate) obtained as tan low melting solid (66mg, 52%). Rf 0.55 (1:4 ethyl acetate/cyclohexane); ^{1}H NMR (300MHz, $CDCl_3$-d1) δ (ppm). 2.28(s, 3H), 6.57(d, 1H), 7.25(d, 2H), 7.35(d, 1H), 7.36(d, 2H). ^{13}C NMR (75MHz, CDCl3-d1) δ (ppm). 27.56, 127.42, 129.14, 129.38, 132.91, 136.21, 141.70, 197.88.

4-Methylbenzelydeneacetone. Prepared as described for **3**; starting from 4-methylbenzyl alcohol (100 mg, 0.83 mmol), after purification with silica gel column chromatography (cyclohexane/ethyl acetate) obtained as yellow low melting solid (68 mg, 52%). Rf 0.65 (1:4 Ethyl acetate/petroleum ether); ^{1}H NMR(300MHz,$CDCl_3$-d1) δ (ppm). 2.33(d, 6H), 6.65(d, 1H),

7.16(d, 2H), 7.42(d, 2H), 7.43(d, 1H); ^{13}C NMR(75MHz, $CDCl_3$-d1) δ (ppm). 21.46, 27.37, 126.19, 128.28, 129.71, 131.64, 140.99, 143.53, 198.44.

3.3.5 One pot synthesis of (±)-warfarin (4).

Benzyl alcohol (100 mg) was added to PEG-400 (5 mL) and stirred for 10 min. Then Fe_3O_4@L-proline/Pd 2 NCs (100 mg) was added and stirred for 10 min. The suspension was further stirred for about 60 h at 60 ^oC under 1 atmospheric pressure of dioxygen. After the disappearance of the starting material, flow of dioxygen was stopped and the reaction vessel was flushed with N_2 gas. To this reaction mass, acetone (5 mL) was introduced and stirred for 5 min under inert atmosphere. The reaction vessel was sealed with rubber septum and stirred at 70^oC for about 24 h. Acetone was removed from the reaction mass under vacuum at 50^oC. At this time, 4-hydroxycoumarin (75 mg) and water (5 mL) were added to the reaction mixture and stirred at 100^oC. After stirring for 12 h the reaction mass was cooled to room temperature, the catalyst was removed magnetically. The product was filtered and recrystallized from acetone / water to give (±)-warfarin, (99 mg) as white solid having 35% overall yield from benzyl alcohol.

3.3.6. Production of (±) – warfarin at pilot plant

To a jacketed glass reactor of 1 L capacity, benzyl alcohol (10g) and PEG-400 (500 mL) were added at ambient temperature and the mass was stirred for 10 min. Further to this was added catalyst Fe_3O_4@L-Proline/Pd 2 NCs (10g) and stirred for 10 min. The reaction mass was heated to 60 ^0C by applying hot water in the reactor jacket. This suspension was stirred for about 60 h at 60° C under 1 atm pressure of dioxygen. After the disappearance of the starting material, the reaction was cooled to ambient temperature by applying chilled water in the jacket. Dioxygen source was removed and the reaction was flushed with N_2. To this reaction mass, acetone (500 mL) was added and was stirred for 5 min under nitrogen atmosphere. The reactor was closed and stirred at 70° C for about 24 h. Acetone was removed from the reaction mass by applying vacuum of about 100 milibar at 50^oC. The distilled acetone was collected in receiver for next cycle. 4-Hydroxy coumarin (7.5g), and water (500 mL) were added to the reaction mass and stirred at 100^oC. After stirring for 12 h the reaction mass was cooled to room temperature by applying chilled water circulation in the reactor jacket, the catalyst was removed by specially designed neutch filter having magnetic bars. The clear solution was

dumped in 500 g ice. The product was filtered and recrystallized from acetone / water to give (±) - warfarin 12.3g as white solid having 43% overall yield from benzyl alcohol.

3.3.7 ^{1}HNMR and ^{13}CNMR of the synthesized compounds:

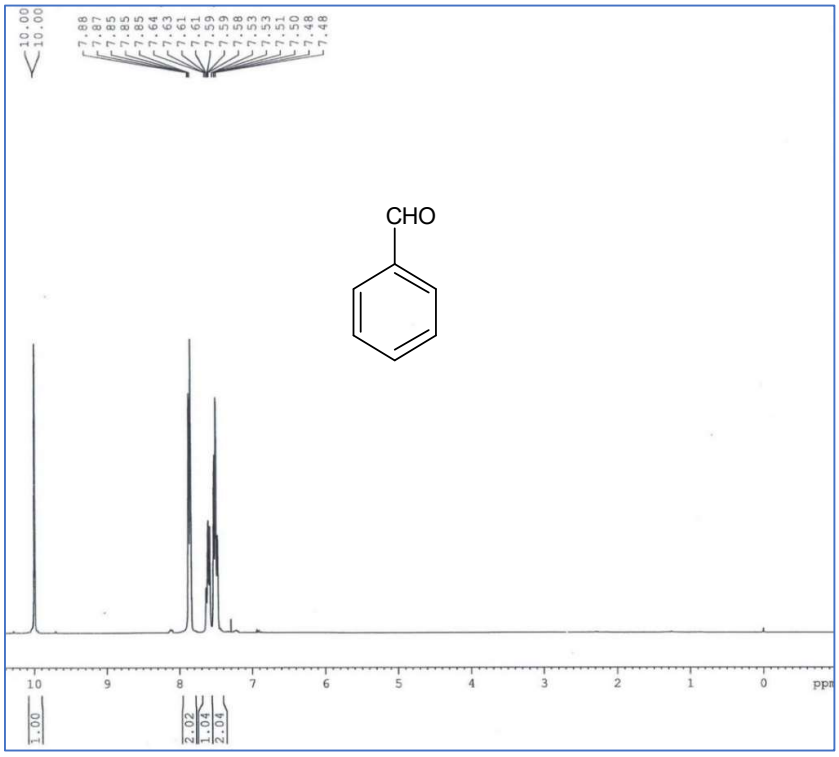


Fig. 8. ^{1}H NMR of Benzaldehyde

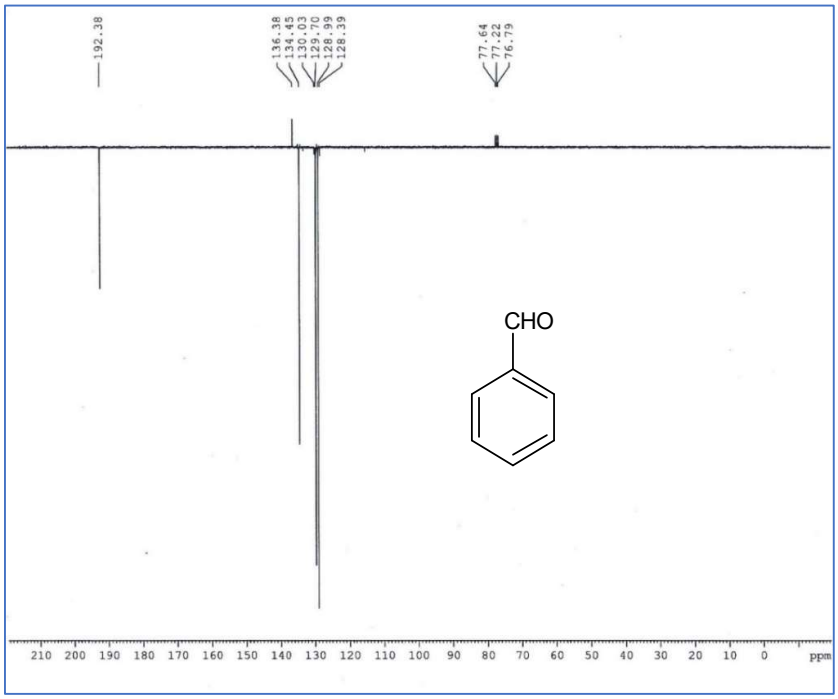


Fig. 9. ^{13}C NMR of Benzaldehyde

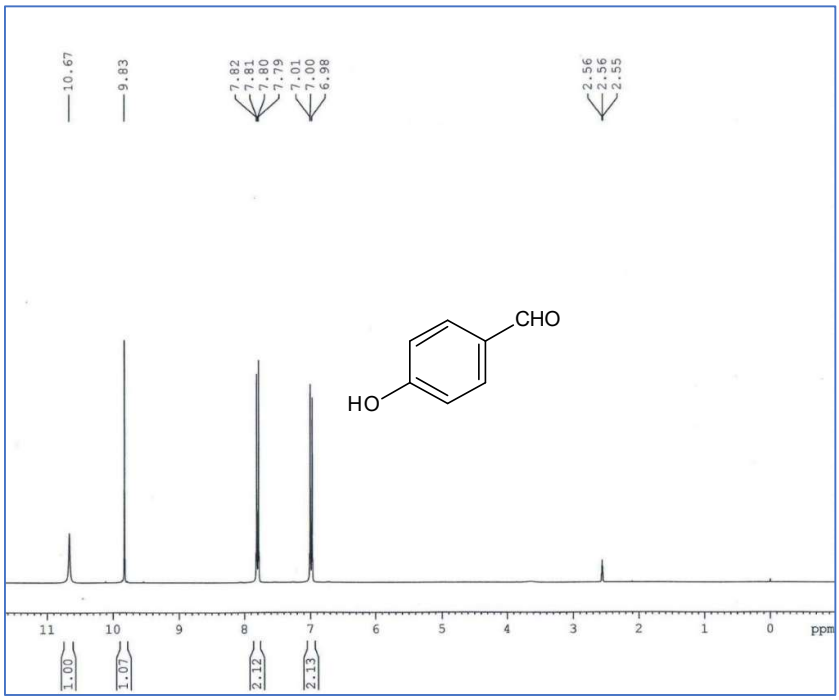


Fig. 10. ^{1}H NMR of p-Hydroxybenzaldehyde

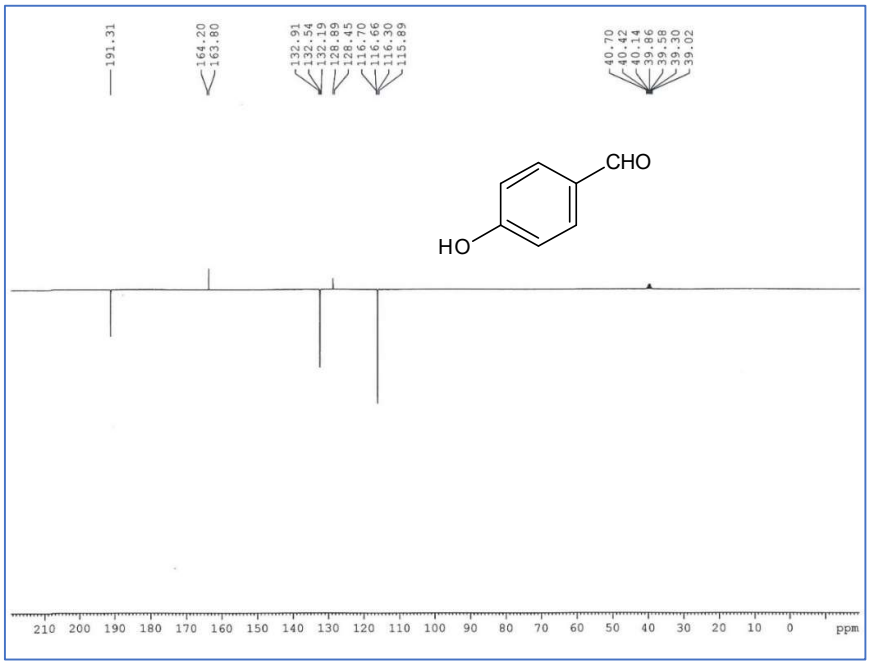


Fig. 11. ^{13}C NMR of p-Hydroxybenzaldehyde

Fig. 12. ^{1}H NMR of p-Chlorobenzaldehyde

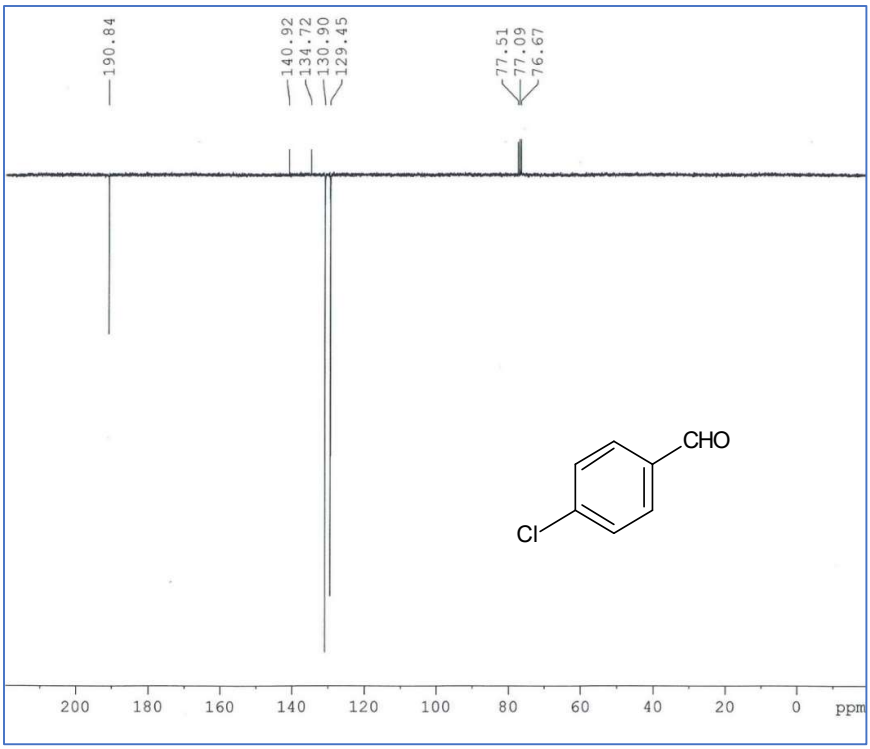


Fig. 13. ^{13}C NMR of p-Chlorobenzaldehyde

Fig. 14. ^{1}H NMR of p-Methoxybenzaldehyde

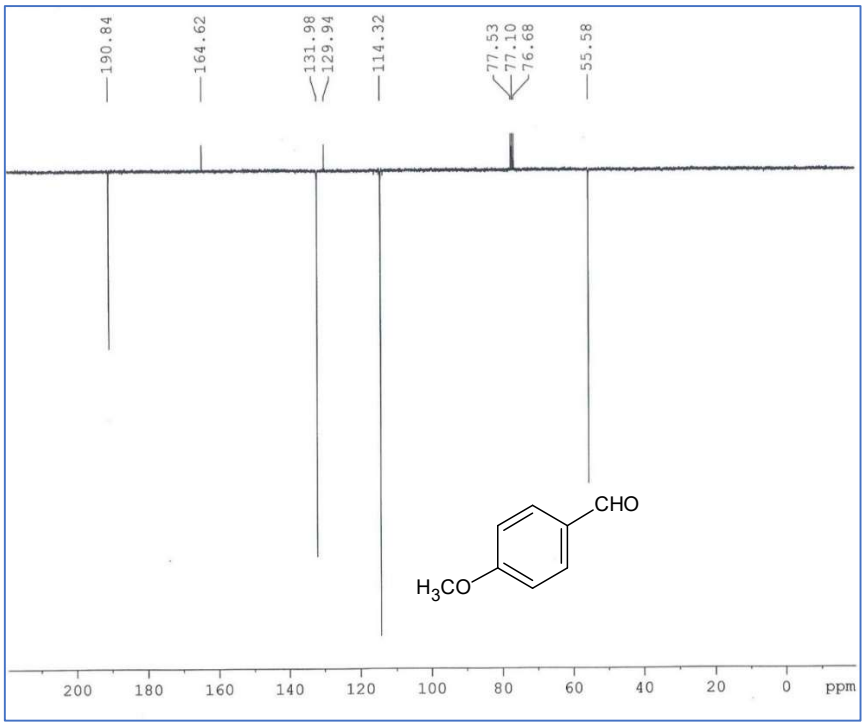


Fig. 15. ^{13}C NMR of p-Methoxybenzaldehyde

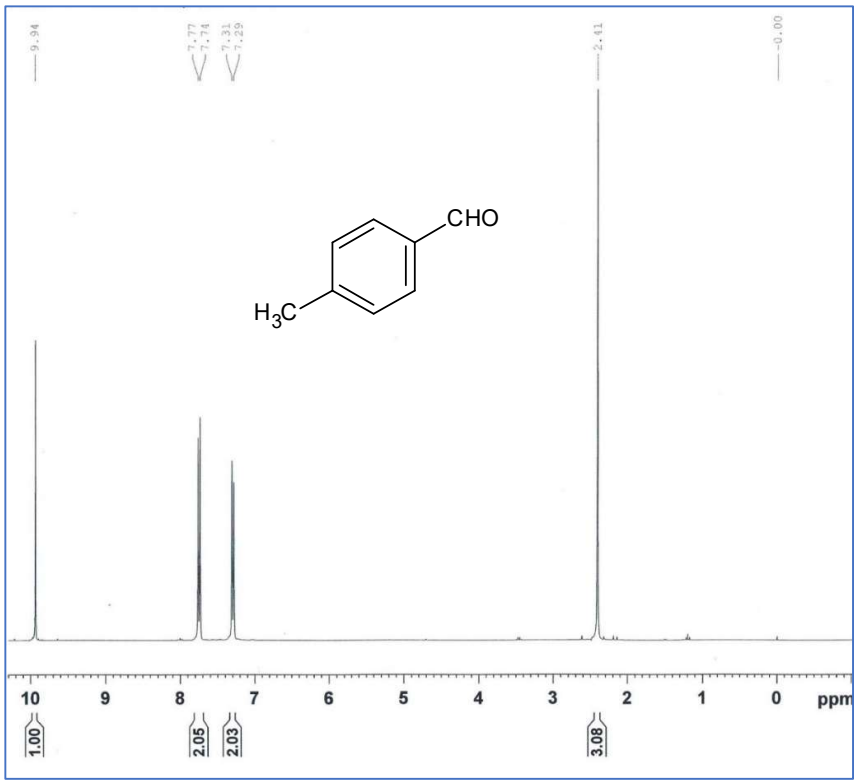


Fig. 16. ^{1}H NMR of p-Methylbenzaldehyde

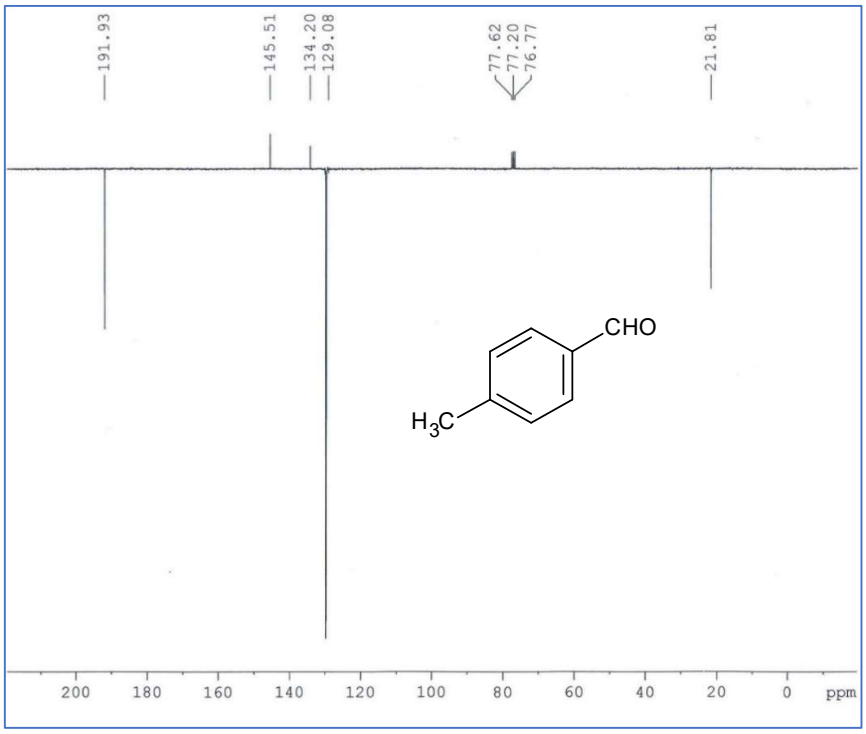


Fig. 17. ^{13}C NMR of p-Methylbenzaldehyde

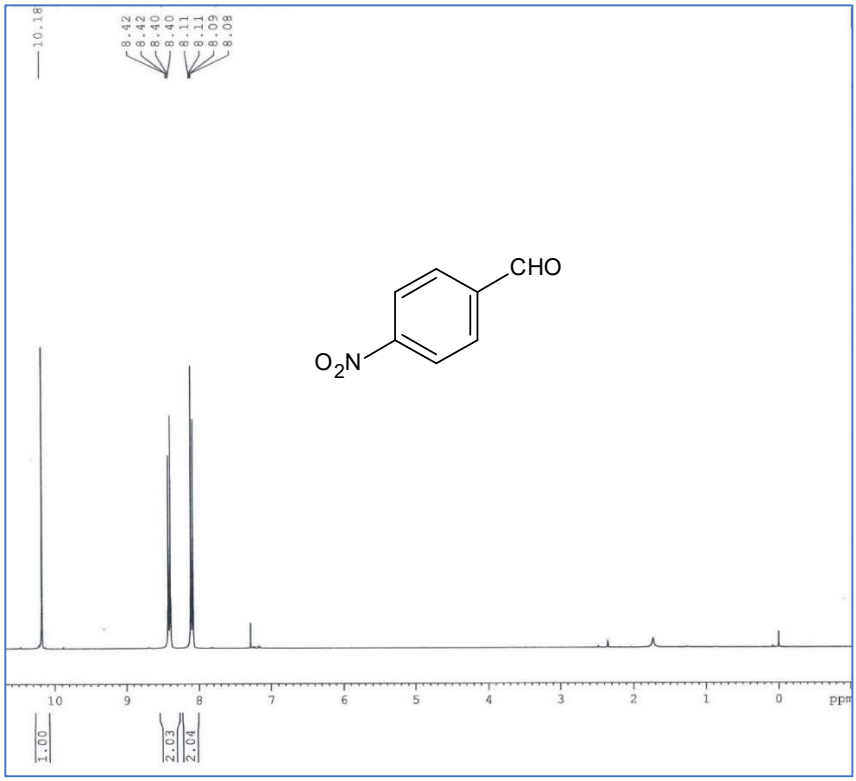


Fig. 18. ^{1}H NMR of p-Nitrobenzaldehyde

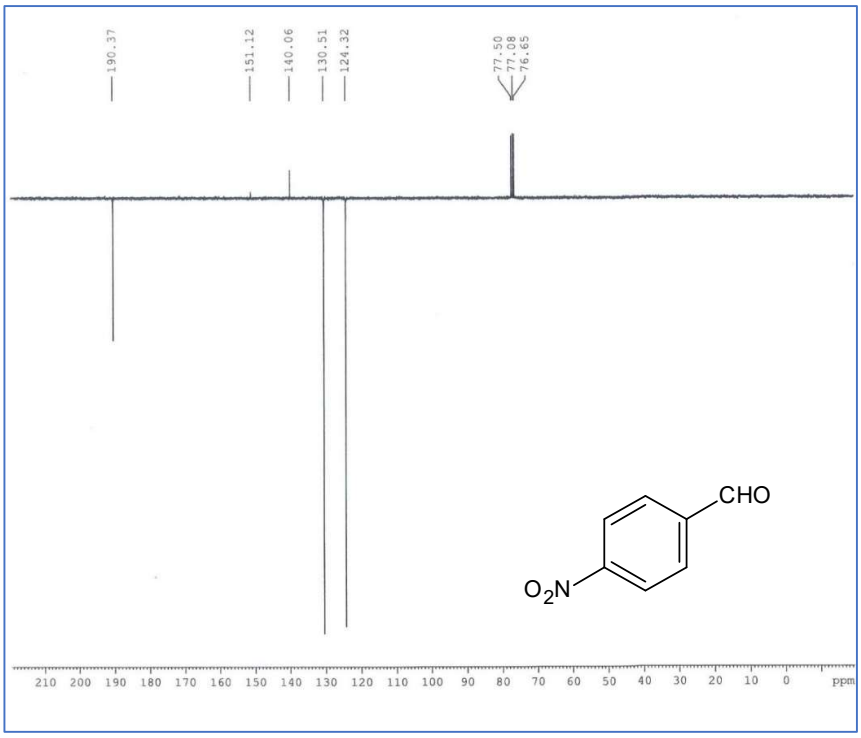


Fig. 19. ^{13}C NMR of p-nitrobenzaldehyde

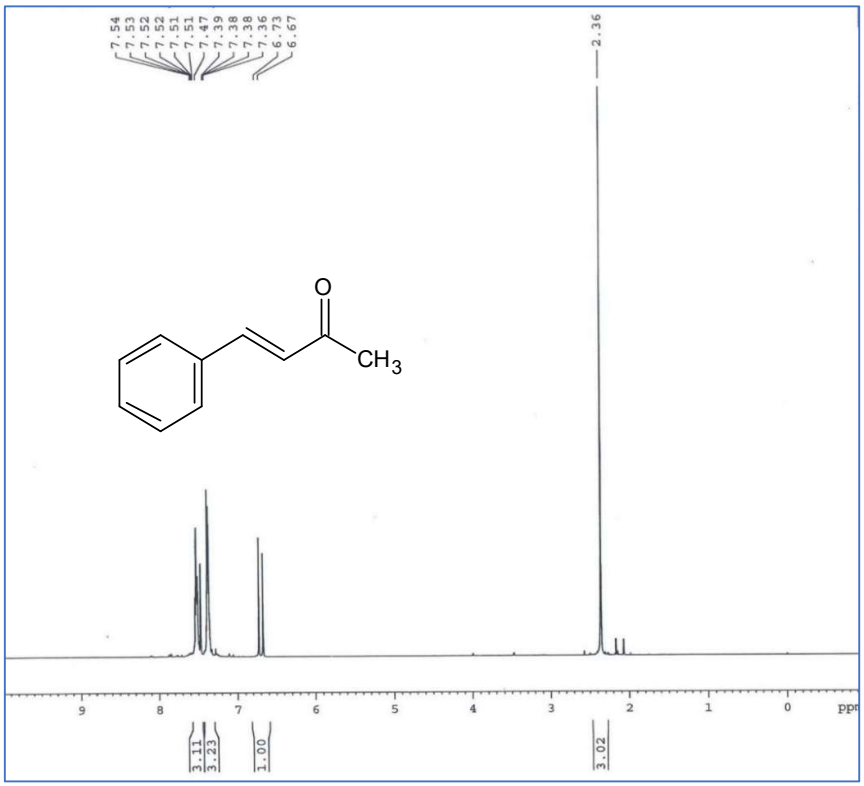


Fig. 20. ^{1}H NMR of (3*E*)-4-phenylbut-3-en-2-one

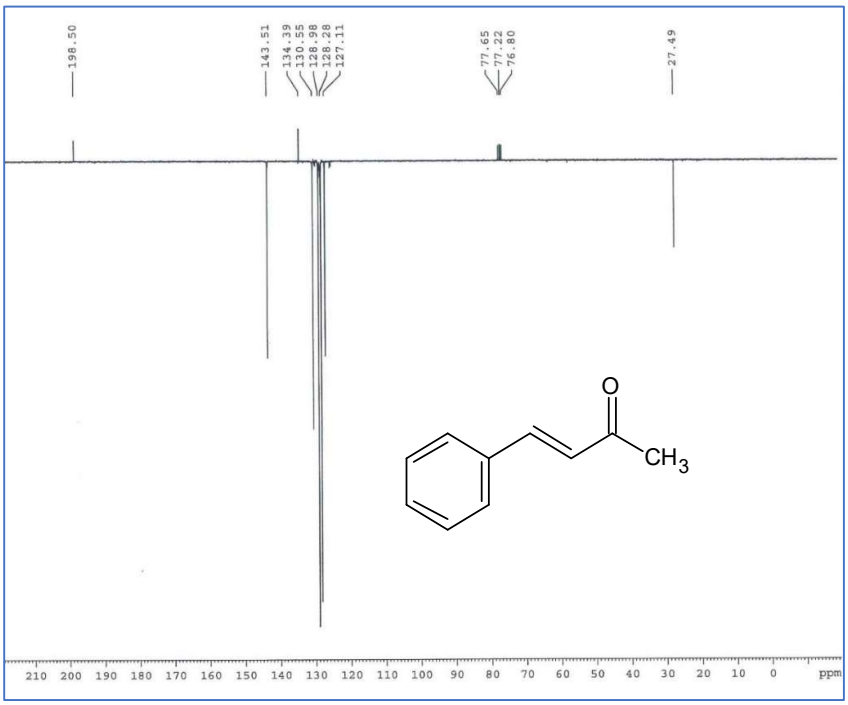


Fig. 21. ^{13}C NMR of (3*E*)-4-phenylbut-3-en-2-one

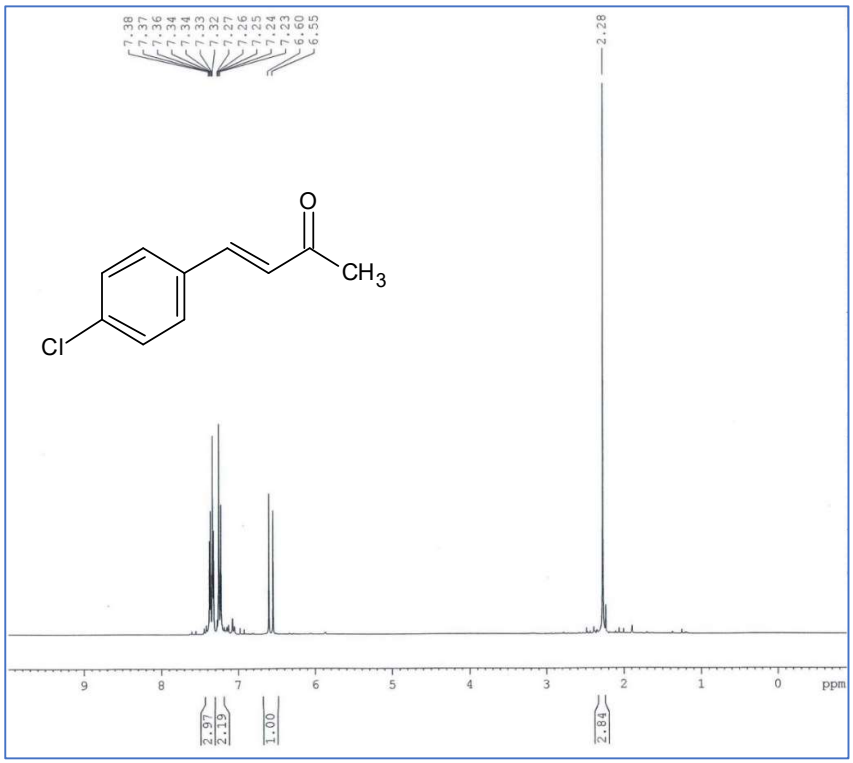


Fig. 22. ^{1}H NMR of (3*E*)-4-(4-chlorophenyl)but-3-en-2-one

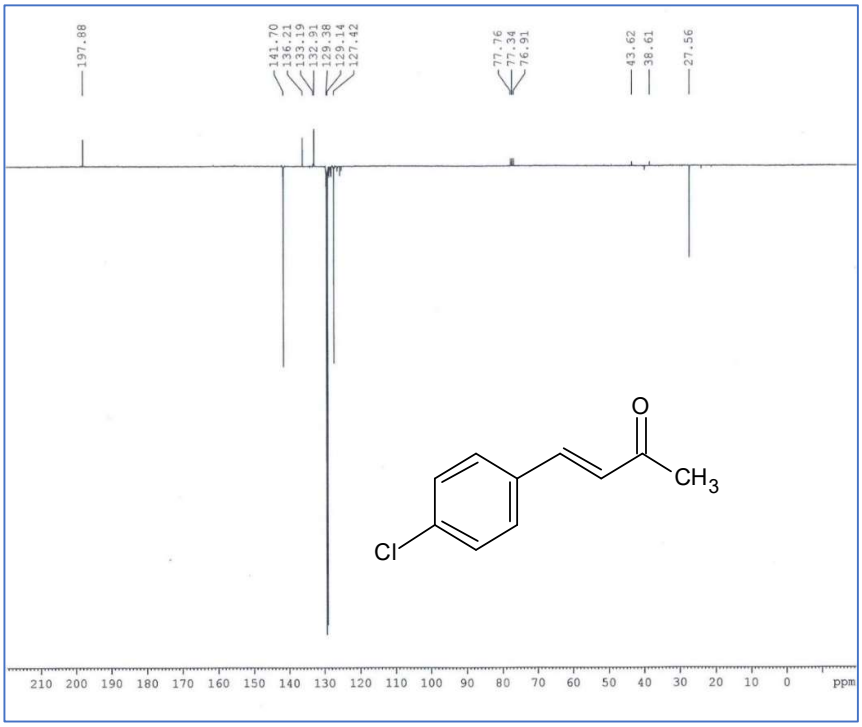


Fig. 23. ^{13}C NMR of (3*E*)-4-(4-chlorophenyl)but-3-en-2-one

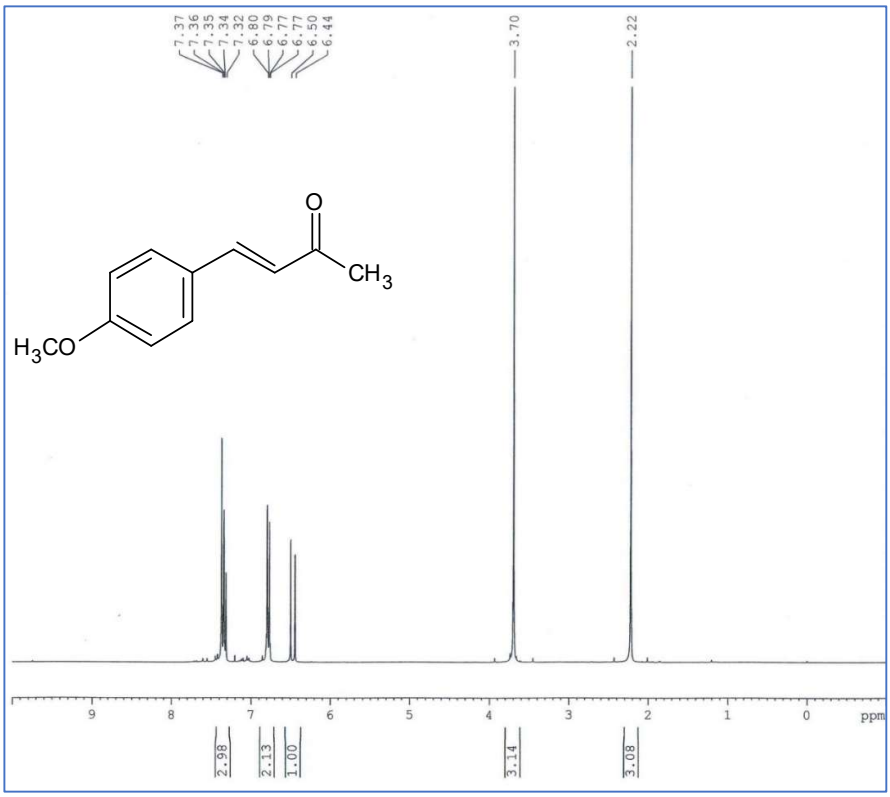


Fig. 24. ^{1}H NMR of (3*E*)-4-(4-methoxyphenyl)but-3-en-2-one

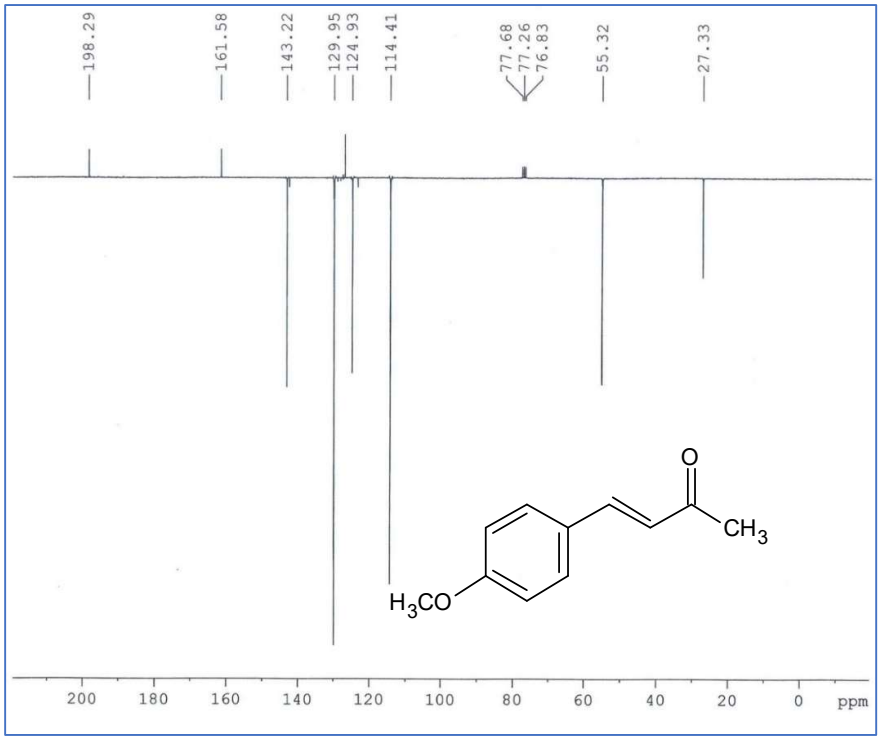


Fig. 25. ^{13}C NMR of (3*E*)-4-(4-methoxyphenyl)but-3-en-2-one

Fig. 26. ^{1}H NMR of (3*E*)-4-(4-methylphenyl)but-3-en-2-one

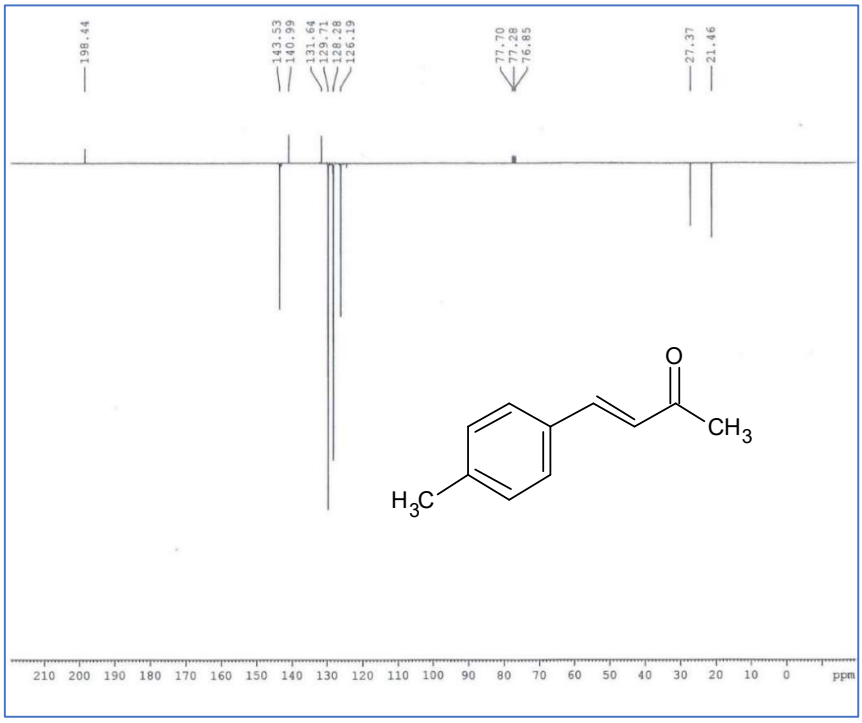


Fig. 27. ^{13}C NMR of (3*E*)-4-(4-methylphenyl)but-3-en-2-one

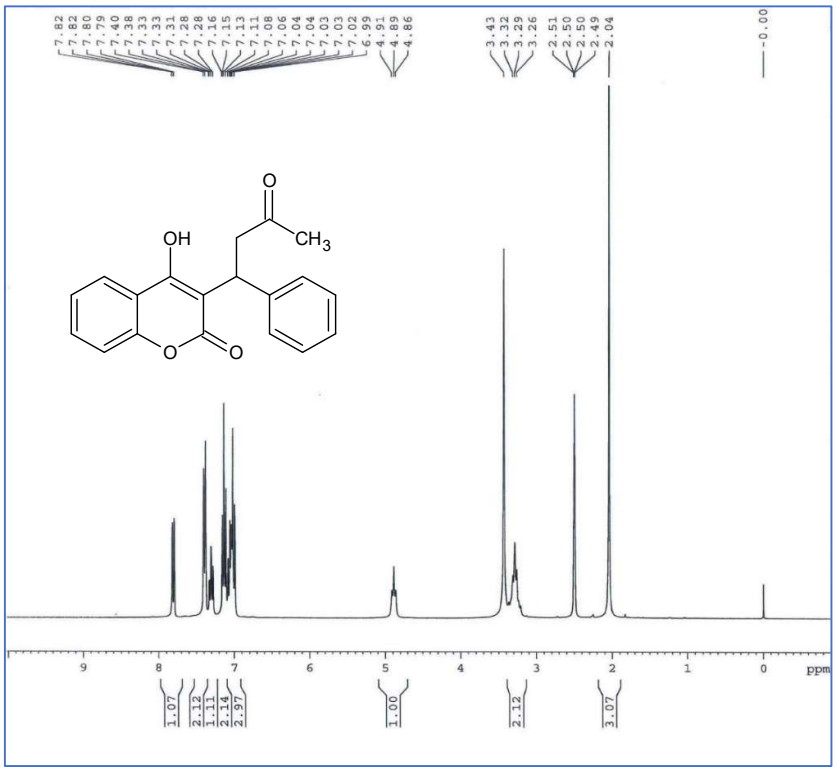


Fig. 28. ^{1}H NMR of Warfarin

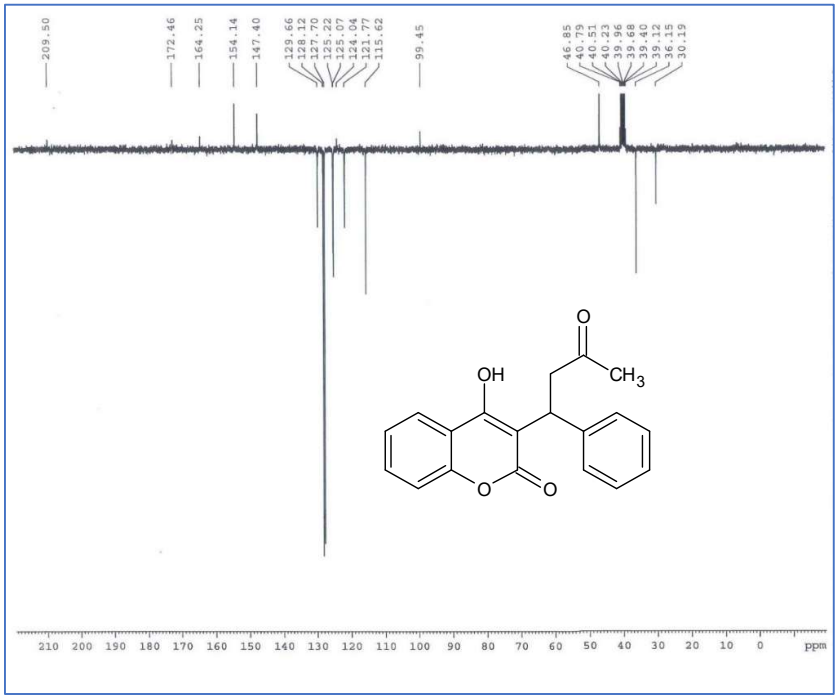


Fig. 29. ^{13}C NMR of Warfarin

3.4 Conclusion

By implementing all the optimized process parameters for the pilot-scale production of (±) – warfarin, it can be concluded that (i) the developed process becomes cost effective compared to others based on bared noble metal catalysts (ii) the catalyst recovery becomes easy by applying magnetic field (iii) the possibility of noble metal leaching from NCs is nullified in the process as no strong base is used at any stage (iv) the as-synthesized catalyst NCs maintained its efficiency for three cycles (under this study) for 3-way catalysis (v) the reaction is 'green' as no noxious solvents are used and the whole one pot process can be carried out in PEG-400 and water as the reaction medium. This study opens new avenues for the development of multicomponent catalysts to produce materials on large scale in a 'green way'. The next study would be the development of tandem process for the large scale production of enantiopure warfarin by loading chiral 1° diaryldiamines on the magnetic host surface with palladium.

3.5 Abbreviations

Fe_3O_4 @L-proline NPs: L-proline capped Fe_3O_4 nanoparticles.

Fe_3O_4 @L-proline/Pd NCs: L-proline capped and Pd loaded Fe_3O_4 nanocomposites.

Reaction-I: Oxidation of benzyl alcohol to benzaldehyde.

Reaction-II: Aldol condensation of benzaldehyde with acetone.

3.6 References

1. N. Halland, T. Hansen and K. A. Jørgensen, *Angew. Chem. Int. Ed.*, 2003, **42**, 4955 – 4957.
2. J.-W. Xie, L. Yue, W.Chen, W. Du, J. Zhu,J. -G. Deng and Y.-C. Chen, *Org. Lett.,* 2007, **9**, 413–415.
3. H. Kim, C. Yen, P. Preston and J. Chin, *Org. Lett.,* 2006, **8**, 5239 –5242.
4. R. M. de Figueiredo and M. Christmann, *Eur. J. Org. Chem.,* 2007, 2575 –2600.
5. T. Meinertz, W. Kasper,C. Kahl, E. Jahnchen, *Br. J. Clin. Pharmacol*., 1978, **5**, 187 -188.
6. R. A. O'Reilly, *N. Engl. J. Med.,* 1976, **295**, 354 -357.
7. L. B. Wingard, R. A. O'Reilly andG. Levy, *Clin. Pharmacol. Ther.,* 1978, **23**, 212 -217.

8. For a review of alcohol oxidation, see: A. M. F. Phillips, A. J. L. Pombeiro, M. N.Kopylovich, *ChemCatChem,* 2017, **9**, 217 – 246.

9. J. Muzart, *Tetrahedron*, 2003, **59**, 5789 –5816.

10. G. Tojo and M. Fernández, In Oxidation of alcohol to aldehyde and ketones: A guide to current common practice, Springer, USA, 2006.

11. K. Sato, M. Aoki and R. Noyori, *Science*,1998, **281**,1646 -1647.

12. B. M. Trost, *Science*, 1991, **254**,1471 -1477; *Angew. Chem., Int. Ed. Engl.,*1995, **34**, 259 - 281.

13. J. –E. Backvall, R. L. Chowdhury and U. Karlsson, *J. Chem. Soc., Chem. Commun.,*1991,473.

14. K. P. Peterson and R. C. Larock, *J. Org. Chem.*,1998, **63,** 3185 -3189.

15. G. -J. ten Brink, I. W. Arendsand R. A. Sheldon, *Science*, 2000, **287**, 1636 -1639.

16. J. A. Cella, J. A. Kelley and E. F. Kenehan, *J. Chem. Soc.,Chem. Commun.,* 1974, 943.

17. J. Muzart, *Tetrahedron*, 2003, **59**, 5789 –5816.

18. X. M. Wang, G. J. Wu, N. J. Guan and L. D. Li, *Appl. Catal. B Environ.,* 2012, **115–116**, 7–15.

19. Y. Su, L. C. Wang, Y. M. Liu, Y. Cao, H. Y. He and K. N. Fan, *Catal. Commun.*, 2007, **8,** 2181–2185.

20. M. Sono, M. P. Roach, E. D. Coulter and J. H. Dawson, *Chem. Rev.,*1996, **96**, 2841 −2887.

21. D. I. Enache, J. K. Edwards, P. Landon, B. Solsona-Espriu, A. F. Carley, A. A. Herzing, M. Watanabe, C. J. Kiely, D. W. Knight and G. J. Hutchings, *Science,* 2006, **311**, 362 -365.

22. F. Zamani and S. M. Hosseini, *Catal.Commun.,* 2014, **43**, 164–168.

23. X. Wang, G. Wu, N. Guan, L. Li, *Appl. Catal. B Environ.,* 115– 116 (2012) 7– 15.

24. T. K. Hollis and B. Bosnich, *J. Am. Chem. Soc.,* 1995, **117**, 4570 -4581.

25. T. Bach, *Angew. Chem., Int. Ed. Engl*., 1994, **33**, 417 -419.

26. A. Erkkilä, I. Majander, and P. M. Pihko, *Chem. Rev.,* 2007, **107**, 5416 –5470.

27. P. Clapés, J. Joglar, In Modern Methods in StereoselectiveAldol Reactions, Ed. R.Mahrwald, Ch. 8. Enzyme-Catalyzed Aldol Additions, Wiley-VCH Verlag GmbH & Co. KGaA, 2013, pp. 475-527.

28. J. Wagner, R. A. Lerner, C. F. Barbas III, *Science,* 1995, **270**, 1797-1800.

29. B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.,* 2000, **122**, 2395 -2396.

30. R. Jenkins and R. L. Snyder, Introduction to X-ray PowderDiffractometry, John Wiley & Sons, NY, 1996.

31. E. Shah and H. P. Soni, *RSC Adv.,* 2013, **3**, 17453 –17461.

32. E. Shah, P. Upadhyay, M. Singh, M. S. Mansuri, R. Begum, N. Sheth and H. P. Soni, *New J. Chem.,* 2016, **40**, 9507 -9519.

33. M. Kakihana, T. Nagumo, O. Makoto and H. Kakihana, *J. Phys. Chem.,* 1987, **91**, 6128 - 6136.

34. J. Chen, S. K. Spear, J. G. Huddleston and R. D. Rogers, *Green. Chem.,* 2005, **7**, 64–82.

35. E. Santaniello, A. Manzocchi and P. Sozzani, *Tetrahedron Lett.,* 1979, **20**, 4581 -4582.

36. S. Chandrasekhar, Ch. Narsihmulu, B. Saritha and S. S. Sultana, *Tetrahedron Lett*., 2004, **45**, 5865 -5867.

37. S. Chandrasekhar, Ch. Narsihmulu, S. S. Sultana and N. R. Reddy, *Org. Lett.,* 2002, **4**, 4399 -4401.

38. S. Chandrasekhar, Ch. Narsihmulu, S. S. Sultana and N. R. Reddy, *Chem. Commun.,* 2003, 1716 -1717.

39. Y. -Q. Cao, Z. Dai, R. Zhang and B. -H. Chen, *Synth. Comm.,* 2005, **35**, 1045 -1049.

40. S. Chandrasekhar, N. R. Reddy, S. S. Sultana, Ch. Narsihmulu and K. V. Reddy, *Tetrahedron*, 2006, **62**, 338 –345.

41. M. S. Kwon, N. Kim, S. H. Seo, I. S. Park, R. K. Cheedrala and J. Park, *Angew. Chem. Int. Ed.*, 2005, **44**, 6913 –6915.

42. K. Motokura, D. Nishimura, K. Mori, T. Mizugaki, K. Ebitani and K. Kaneda, *J. Am. Chem. Soc.,* 2004, **126**, 5662 – 5663.

43. L. Yanan and C. Daoyong, *Chin. J. Chem.,* 2011, **29**, 2086 -2090.

44. T. E. Kristensen, K. Vestli, F. K. Hansen and T. Hansen, *Eur. J. Org. Chem.,* 2009, 5185–5191.